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One- or two-stage cervical esophagocolostomy or ileostomy for replacement of the esophagus

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Today, many surgeons utilize the colon for replacement of the esophagus when the latter organ has been destroyed by malignant tumors or extensive scarring. Vulliet,[19] Kelling,[4] Thorek,[17] and von Hacker[18] were the first to employ the large bowel for this purpose. Since then numerous reports of this technique of esophageal replacement have appeared in the literature, many of which told of excellent results. The present report is written to emphasize the advantage of a cervical ileostomy or colostomy when the colon is utilized for this purpose.

Wide vascular arches in the mesentery facilitate transposition of an isolated segment of colon to the cervical region without compromise of its blood supply. However, all possible varieties of distribution of the colic vessels must be considered and the difficulties which may arise because of them anticipated.

Various portions of the colon may be utilized. The right colon, which can be placed in an isoperistaltic position, has been employed by many surgeons (Kelling,[4] Thorek,[17] Roith,[14] Rudler,[15] Lafargue,[5] Lortat-Jacob,[7] and others). Transplantation of the right colon depends on the course of the right colic artery and in many instances this is quite variable. The transverse or left colon can also be easily transposed into the chest either in an isoperistaltic or antiperistaltic position with preservation of an adequate blood supply. Continuity between the esophagus and transplanted loop of the colon can be established in one or two stages by an end-to-end or end-to-side anastomosis.

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CLINICAL MATERIAL

We have utilized the colon for esophageal replacement in 21 patients with cicatricial stenosis or malignant disease of this organ (Table I).

Esophageal replacement by colon. A total of 4 of the 21 patients died postoperatively. The death which occurred after operation for cicatricial stenosis was due to peritonitis. The 3 deaths which occurred after operation for cancer of the esophagus were caused by malignant cachexia.

Table I

	No. of patients	*Deaths*
Cicatricial stenosis of esophagus	10	1
Cancer of esophagus	11	3
Totals	21	4

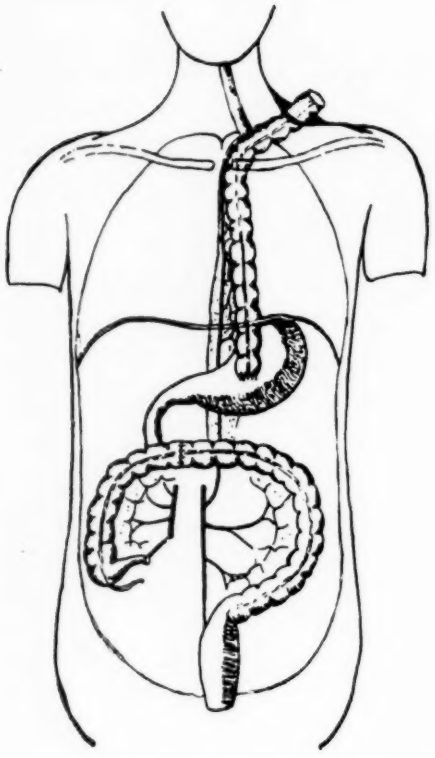

Fig. 1. Diagrammatic illustration of use of free end of loop for temporary cervical colostomy or ileostomy.

In 12 patients the right colon was transposed and in 6 the transverse colon was utilized. In each of these 18 patients the right colic artery was preserved to insure the blood supply to the isolated part. The right colon was placed in an isoperistaltic position in every instance, but an antiperistaltic placement of the colon was carried out in the 6 patients in whom the transverse colon was utilized. In the remaining 3 patients, the transverse colon was placed in an isoperistaltic position with the left colic artery preserved as the blood supply to the loop.

In no instance was there failure due to necrosis of the transplanted loop of intestine from inadequate blood supply. Careful observation of the circulation of the transplanted loop prior to and during the process of bringing it up into the chest and careful preservation of blood supply insured vascular adequacy. The isolated loop was brought up either subcutaneously or by a retrosternal or transpleural route.

Continuity of the alimentary tract was re-established by end-to-end colic anastomosis or by side-to-side ileocolic anastomosis in instances when the right colon was utilized. The distal end of the isolated loop was implanted end-to-side into the stomach or the proximal jejunum. The proximal end of the loop was anastomosed side-to-end to the transected cervical esophagus in one or two stages. The free end of the loop was used for temporary cervical colostomy or ileostomy in order to allow passage of a feeding catheter into stomach or jejunum (Figs. 1 and 2).

DISCUSSION

Use of a cervical colostomy or ileostomy in patients with replacement of the esophagus by colon has, to our knowledge, not been previously reported in the literature. The procedure is recommended for several reasons. (1) A gastrostomy or jejunostomy for feeding the patient during the postoperative period is avoided. (2) If such a gastrostomy or jejunostomy has been carried out as a preliminary step to esophageal replacement, it can be closed during the replacement operation. (3) The method offers an additional protection against the insufficiency of the esophagoileal or esophagocolic anastomosis in that the healing of the anastomosis is not disturbed by the passage of food. (4) If improper healing of the anastomosis should develop, sufficient length of the transplanted loop is available for the performance of a new anastomosis at a higher level. (5) Cervical ileostomy or colostomy is easily closed in a second stage by simple suture after healing of the esophagocolic anastomosis and as soon as the patient

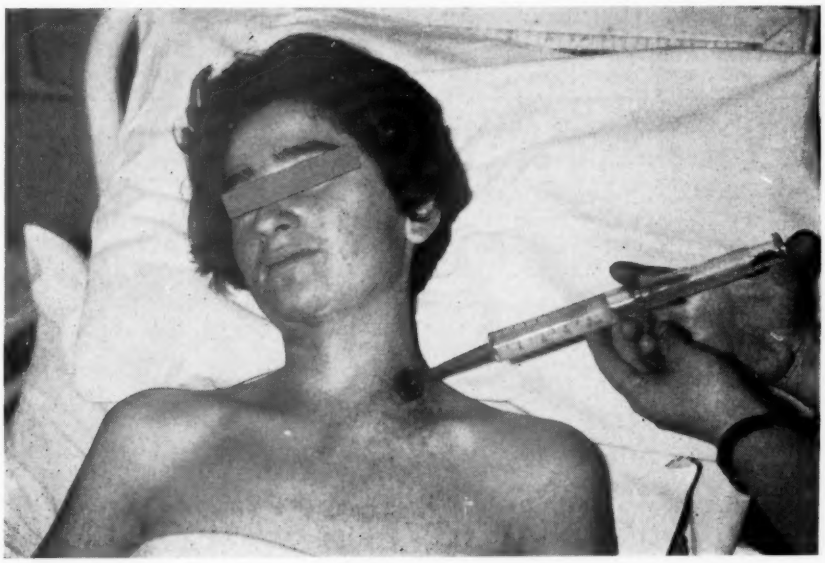

Fig. 2. Use of the temporary cervical colostomy or ileostomy for feeding.

has recovered adequately. We believe this procedure prevents inadequate healing at the esophagocolic anastomosis.

SUMMARY

Twenty-one patients have been operated upon and replacement of the esophagus by the colon carried out. In 10 patients the operation was performed for cicatricial stenosis and in 11 for cancer of the esophagus.

An end-to-side anastomosis of the intestine with the cervical esophagus to the bowel was carried out and the end of the colon or ileum was then implanted in the side of the neck to allow the introduction of a feeding catheter into the stomach or jejunum.

This method affords several advantages during the early postoperative period and, we believe, simplifies the operative technique. The immediate and late results of replacement of the esophagus by this method have been excellent.

The authors wish to thank Dr. John F. Perry, Jr., of the Department of Surgery at the University of Minnesota, for his help in revising the paper.

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Fecal excretion of fat and nitrogen after esophagogastrectomy in man

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The purpose of this study was to determine the effect of various types of esophagogastrectomy on the intestinal absorption of fat and nitrogen as determined by intake-excretion studies. Although a number of reports are available of studies on fecal excretion after various types of gastric resection and allied procedures on the gastrointestinal tract,[6-8, 16-18, 21, 24] we were able to find only 1 published report concerning such studies in patients who had undergone esophagogastrectomy.[2] Intake-excretion studies on dogs after esophagogastrectomy have been reported by Moser and associates.[15]

MATERIALS AND METHODS

Four groups of patients, each with a different type of esophagogastrectomy, were compared. Twelve operations were performed for benign esophageal stricture, 9 for carcinoma of the lower part of the esophagus or the esophagogastric junction, and 1 for esophageal varices; 22 patients were studied. None of the patients operated on for carcinoma showed evidence of recurrence at the time they were studied, although many of them eventually died from recurrent tumors or metastatic lesions. The 4 groups were established according to the operations performed. Patients in Group 1 had undergone esophagogastrectomy without any other procedure (5 patients); those in Group 2, esophagogastrectomy with pyloromyotomy (5 patients); those in Group 3, esophagogastrectomy with an Allison Roux Y anastomosis (4 patients); and those in Group 4, esophagogastrectomy with antral resection (8 patients). The latter operation has been proposed and carried out by one of us (Ellis) and has been fully described previously.[3, 4]

The studies were carried out at intervals of time after operation varying from 1 to 16½ months. All patients except 4 were studied between 3 and 8½ months after operation. Two of the 4 patients were studied sooner after operation than this (1 and 2½ months, respectively), and the other 2 were studied later (10 and 16½ months, respectively).

Intake-excretion studies were performed while the patients consumed a standard test diet containing 101.6 Gm. of fat, 117.5 Gm. of protein, and 270 Gm. of carbohydrate per day. The details of this diet have been published.[23] The period of study was 6 days in all instances but one in which the patient was studied for only 3 days. The patients started eating the diet at least 1 day before the test commenced and continued to take it until the test was completed. Only those who ate all the food served them throughout the test were included in this study. Collection of feces was regulated by the use of carmine markers administered before breakfast at the beginning and at the end of each

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Table I. *Total solids, fat, and nitrogen in feces of healthy persons on moderately high-fat diet**

Subject No.	Total solids (Gm./day)	Fat			Nitrogen (Gm./day)
		Gm./day	% of total fecal solids	% of ingested fat	
1	23.7	4.7	19.6	4.6	1.6
2	39.1	6.4	16.3	6.3	2.4
3	13.6	1.8	13.3	1.8	0.8
4	28.9	4.2	14.6	4.1	1.6
5	25.4	2.6	10.0	2.6	1.6
6	27.5	3.7	13.3	3.6	1.6
7	20.1	3.8	19.0	3.7	1.1
8	37.3	5.4	14.5	5.3	2.5
9	31.4	6.7	19.3	6.6	1.6
10	27.7	2.6	9.3	2.6	1.7
11	29.2	2.9	9.9	2.9	2.0
Averages†	27.6	4.1	14.5	4.0	1.7
	(13.6-39.1)	(1.8-6.7)	(9.3-19.6)	(1.8-6.6)	(0.8-2.5)
Standard deviation	7.2	1.6	—	—	0.49
Standard error of mean	2.2	0.48	—	—	0.15

Modified from Table 5, Wollaeger and associates.[23]

*The diet included 101.6 Gm. of fat, 117.5 Gm. of protein (18.8 Gm. of nitrogen), and 270 Gm. of carbohydrate per day.

†Numbers in parentheses are ranges.

period of study. Feces colored by the first marker were included in the collection, whereas those stained by the second marker were excluded. Analysis of the stools was made for the entire period and the daily values for fecal solids, fat, and nitrogen were obtained by averaging. Determinations of fecal fat were carried out by the Saxon method and the values for fecal and urinary nitrogen were determined by the Kjeldahl procedure.

RESULTS

Eleven normal persons had been studied previously under the same conditions while eating the same diet. The results of this study have been reported in detail[23] and the data obtained on this normal group are summarized in Table I. The results obtained in the present series of 22 patients who had undergone various types of esophagogastrectomy are presented in Table II.

Excretion of fecal fat. Loss of fat in the feces of the normal persons varied from 1.8 to 6.7 Gm. per day, averaging 4.1 Gm., or approximately 4 per cent of the fat intake (Table I). Compared to normal persons, the patients who had undergone esophagogastrectomy lost excessive amounts of fat in the feces, as seen in Fig. 1 and in Table II. The difference between the means of the 2 groups was highly significant ($P < 0.001$). In only 1 patient (Case 19, Group 4) were the losses of fat within the range of normal values. No great difference was evident in the average loss of fat between various groups of patients who had undergone esophagogastrectomy, although pronounced individual differences occurred within groups among both control and surgical patients.

Total fecal solids. The total fecal solids of the normal group averaged 27.6 Gm. per day. Among all the patients who had undergone esophagogastrectomy (Table II), the value for total solids was significantly greater, averaging 35.9 Gm. per day ($0.05 > P > 0.02$). The number of patients in each of the 4 subgroups was too small to permit separate statistical evaluation of the results in each.

Fecal nitrogen. The amount of fecal nitrogen in the normal persons ranged from 0.8 to 2.5 Gm. per day, averaging 1.7 Gm. The average fecal nitrogen in the patients who had undergone esophagogastrectomy (Table II) was somewhat greater (2.02 Gm. per day), but the difference was not signif-

icant ($0.2 > P > 0.1$). It appears likely, however, that study of a larger series of patients after esophagogastrectomy would demonstrate a significant difference from normal. Values for fecal nitrogen greater than any obtained among the normal persons were found in 4 of the surgical patients (Cases 9, 11, 14, and 15).

COMMENT

These results indicate that esophagogastrectomy alone or in addition to other operative procedures on the stomach or upper part of the intestinal tract (pyloromyotomy, Allison Roux Y operation, or antral excision) impairs the intestinal absorption of fat to a significant degree. All but 1 of the 22 patients showed a definite increase in the quantity of fat excreted in the feces. The degree of loss of fat varied considerably from one patient to another, even among those who had undergone the same operation. Such variations have been observed frequently in groups of patients or animals studied in the same manner after partial or total gastrectomy.[24] Even among healthy persons who eat a standard diet, the variation in excretion of fat may be considerable (Table I). No significant differences in the excretion of fat were apparent among the 4 groups of patients studied, although the number of patients in each group was too small for statistical analysis. An attempt was made to correlate the clinical symptoms of inability

Table II. *Fecal excretion in 22 patients after esophagogastrectomy*

Group	*Case No.*	*Time after operation, (mo.)*	*Amount of stomach removed*	*Fat (Gm./day)*	*Total solids (Gm./day)*	*Fat (% of total fecal solids)*	*Nitrogen (Gm./day)*
1. Esophagogastrectomy (EG) without pyloromyotomy	1*	3	3/4	7.2	34.8	29.0	1.46
	2*	4	1/3	12.0	33.8	35.3	1.97
	3*	3	4/5	8.5	26.3	32.4	1.23
	4*	6	4/5	7.5	21.0	35.7	1.03
	5*	4½	4/5	26.1	—	—	2.45
Averages				12.3	29.0	—	1.63
2. EG with pyloromyotomy	6*	5	4/5	13.0	42.8	30.0	1.75
	7†	8½	4/5	17.0	42.0	40.0	2.03
	8*	1	4/5	16.0	32.4	49.5	2.43
	9*	8	4/5	19.7	40.9	48.2	3.15
	10*	6	4/5	9.6	21.6	44.5	1.15
Averages				15.1	35.9	—	2.10
3. EG with Allison Roux Y	11†	10	1/3	9.9	32.9	30.1	2.86
	12†	6	< 1/4	19.2	39.2	48.9	1.54
	13‡	16½	1/2	21.1	42.8	49.3	2.12
	14†	6	< 1/4	7.7	60.3	12.7	3.37
Averages				14.5	43.8	—	2.47
4. EG with antral excision	15†	6	1/4-1/3	30.5	56.7	53.9	3.38
	16†	6	1/4-1/3	10.6	33.0	32.2	1.70
	17†	6	1/4-1/3	18.3	44.6	41.4	2.42
	18†	3	1/4-1/3	9.6	38.1	25.2	1.94
	19†	4	1/4-1/3	5.4	29.5	18.4	1.52
	20†	5	1/4-1/3	11.6	34.7	33.4	1.68
	21†	3	1/4-1/3	9.9	23.9	41.3	2.00
	22†	2½	1/4-1/3	9.2	21.9	41.9	1.15
Averages				13.1	35.3	—	1.97
Averages, all groups				13.6	35.9	—	2.02
Standard deviation				6.6	10.5	—	0.7
Standard error of mean				1.4	2.3	—	0.15

*Operation performed for carcinoma.

†Operation performed for esophagitis with stricture.

‡Operation performed for esophageal varices.

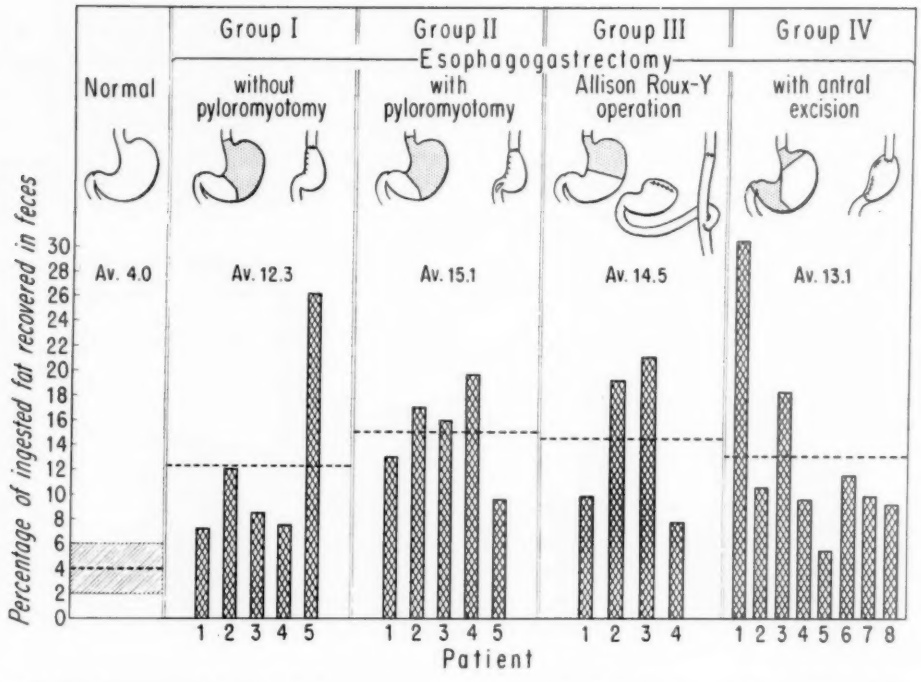

Fig. 1. Amount of ingested fat recovered in feces in 22 patients after various types of esophagogastrectomy.

to maintain weight and the occurrence of diarrhea with the level of excretion of fecal fat. Loss of weight was common among patients of all 4 groups, although it was least severe in Group 4. All the patients in this group had been operated on for benign disease. The patients in this group who had the greatest losses of fecal fat also experienced diarrhea, which in at least 1 instance (Case 15) was a major complaint and constituted a severe handicap. Patients in the other 3 groups did not evidence any clear correlation between failure to gain weight and the degree of excretion of fecal fat. Some patients with pronounced loss of weight had only a slight increase in excretion of fecal fat, and some who maintained their weight had a relatively great loss of fecal fat. In Groups 1, 2, and 3, loss of weight occurred more frequently than it did in Group 4, and it was more pronounced among patients who had malignant disease than in patients operated on for benign lesions. Diarrhea was not a prominent symptom in any of the patients in these 3 groups.

The steatorrhea after esophagogastrectomy is not explained satisfactorily on any single basis, and it probably results from interference with multiple physiologic mechanisms by the surgical procedures. This appears to be true also of the steatorrhea that follows total gastrectomy, and that subsequent to partial gastrectomy in which the distal portion of the stomach is removed and a gastroduodenal or gastrojejunal anastomosis is performed. With respect to these operations, the following disturbances of gastrointestinal function occur and are considered to play a role in postgastrectomy steatorrhea: (1) rapid emptying (loss of reservoir function) of the stomach,[19] (2) intestinal "hurry,"[10] (3) diminished flow of pancreatic secretions or bile because of impairment of the mechanism of stimulation of such flow,[1, 14] (4) insufficient mixing of food with digestive juices (pancreatic secretion and bile) because of shunting of gastric contents past the duodenum,[11, 12, 14, 21] and (5) loss of the digestive and triturating functions of the stomach.[1, 11, 12] It appears likely that some or all of these disturbances also may contribute to the production of steatorrhea in our patients who had undergone esophagogastrectomy.

The demonstration of steatorrhea probably was most likely to be expected in Group 3 of our patients (Allison Roux Y operation), in whom the reservoir, digestive, and triturating functions of the stomach were lost completely, and ingested food was shunted past the duodenum incompletely mixed with bile and pancreatic secretions. From the standpoint of digestive function, patients in this group are in essentially the same situation as are those who have undergone total gastrectomy with esophagojejunostomy. Steatorrhea also is not unexpected in the patients of Group 4, in whom the emptying mechanism of the stomach has been interfered with by removal of the gastric antrum and pylorus. These patients resemble those who have undergone resection of the distal segment of the stomach with a Billroth I type of anastomosis, an operation that is usually followed by impaired capacity to absorb fat.[20, 21]

Patients in Group 2 also have undergone an operation that probably influences gastric emptying, namely, pyloromyotomy. Whether this procedure alone (in the absence of esophagogastrectomy) would increase the rate of gastric emptying and interfere with the reservoir functions of the stomach sufficiently to cause steatorrhea has not been determined. However, Moser and co-workers[15] found that pyloromyotomy increased the excretion of fecal fat in dogs which had undergone resection of the cardia of the stomach as compared to dogs which had been subjected to resection of the cardia alone. Definite steatorrhea was demonstrated in our patients who had pyloromyotomy combined with esophagogastrectomy, including extensive (four-fifths) resection of the proximal part of the stomach.

The occurrence of steatorrhea in Group 1 might not have been expected, since no operative procedure was performed that would directly increase the rate of gastric emptying. Furthermore (as in Groups 2 and 4), gastroduodenal continuity was maintained, so that ingested food, rather than being short-circuited around the duodenum, was afforded adequate opportunity for proper mixture with bile and pancreatic juice. The removal of the proximal portion of the stomach might in itself interfere sufficiently with the digestive, triturating, and reservoir functions of that organ to impose an excessive burden on the digestive functions of the small intestine and thus produce steatorrhea. Clinical and experimental evidence[5] appears to indicate that the gastric remnant left after esophagogastrectomy alone does not empty well, and that gastric retention rather than rapid emptying is the rule. It is for this reason that so-called gastric drainage operations, such as pyloromyotomy, resection of the antrum, or gastroenterostomy, frequently are performed in conjunction with esophagogastrectomy. Therefore, loss of reservoir function (rapid gastric emptying) would not appear to be an important factor in the causation of steatorrhea in Group 1.

The amount of stomach removed has been shown by Moser's group[15] to have a bearing on the degree of steatorrhea produced by esophagogastrectomy with pyloromyotomy in dogs. These investigators found that excretion of fecal fat paralleled the extent of the gastric resection. They did not determine the effect of the extent of gastric resection on the degree of steatorrhea in dogs which did not have pyloromyotomy. That extensive resection of the body of the stomach without resection of the esophagus or cardia does not produce steatorrhea is indicated by the findings of Everson,[7] who performed intake-excretion studies on dogs which had undergone segmental gastric resection. In these operations, the cardia, antrum, and pylorus were all maintained intact. Our patients who had esophagogastrectomy without pyloromyotomy (Group 1) apparently showed no correlation between the amount of stomach removed and the degree of steatorrhea (Table II).

Since esophagogastrectomy cannot be performed without severing both vagus nerves, it is necessary to consider the role of vagotomy as a causative factor in the production of steatorrhea in our cases. The results of intake-excretion studies in dogs after vagotomy indicate that steatorrhea is not caused by this operation if it is not combined

with some other surgical procedure on the stomach.[13, 20] Similar results were noted by one of us[22] in 2 patients after bilateral vagotomy for duodenal ulcer. On the other hand, Fox and Grimson[9] found increased values for fecal fat in 3 patients who had undergone vagotomy without any associated gastric operation and who were experiencing symptoms suggestive of intestinal dysfunction. Although few intake-excretion studies have been carried out on vagotomized human subjects, the weight of evidence presently available indicates that vagotomy alone does not often cause steatorrhea. However, the results of a number of studies indicate that the degree of steatorrhea after gastric resection[6, 13, 18] and gastroenterostomy[13] is increased by vagotomy. Moser's group found that pyloromyotomy produced steatorrhea in vagotomized dogs, which do not ordinarily show this abnormality.[13, 20] These findings suggest that, although vagotomy alone usually does not produce steatorrhea, it may make manifest a latent tendency to steatorrhea resulting from some other operation on the upper part of the gastrointestinal tract, or it may increase the degree of steatorrhea already produced by such an operation. It appears probable that in this way vagotomy plays a part in the causation of steatorrhea in patients who have undergone esophagogastrectomy.

SUMMARY AND CONCLUSIONS

Intake-excretion studies of fat and nitrogen with the aid of a standard test diet were carried out at the Mayo Clinic on 4 groups of patients, each of which had undergone a different type of esophagogastrectomy. Results were compared with those from study of healthy persons who ate the same test diet.

All but 1 of the total of 22 surgically treated patients studied lost excessive quantities of fat in the feces, and the difference between the mean of this group and that of the healthy controls was highly significant ($P < 0.001$). No great difference occurred in the average loss of fat among the 4 groups of patients who had undergone esophagogastrectomy.

Fecal total solids were significantly increased among patients subjected to esophagogastrectomy, but the increase in fecal nitrogen was not statistically significant. However, 4 of the 22 patients had values for fecal nitrogen above the normal range.

It appears likely that the steatorrhea after esophagogastrectomy results from interference with multiple physiologic mechanisms by the surgical procedures. The causative factors are probably much the same as those which produce steatorrhea after total gastrectomy or partial gastrectomy in which the distal portion of the stomach is removed and a gastroduodenal or gastrojejunal anastomosis is performed.

The evidence presented suggests that vagotomy plays a role in causing the steatorrhea that follows esophagogastrectomy.

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Intestinal decompression: use of a long tube with a coiled spring for relief of distention without enterotomy or enterostomy

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Decompression, however achieved, has been and will always remain the mainstay of treatment for acute intestinal obstruction. Through the past 3 decades there has been a considerable lowering of the mortality rate of patients with this serious disorder. When surgeons can deal with the distended bowel as though distention were not present, the mortality rate of patients with acute intestinal obstruction will approximate that of patients who undergo elective operations for relief of a similar condition.

Over a period of 35 years there has been a continuous interest in the bowel obstruction problem in this clinic. During this time, a number of operative as well as nonoperative techniques of intestinal decompression have been described.[3]

The technique to be described began as an attempt to extend nonoperative methods of achieving decompression. The Grafton Smith technique of intestinal intubation, originally described by Smith and Brackney,[2] has undoubtedly been the quickest method of passing a long intestinal tube well into the duodenum or to the duodenojejunal angle or just beyond it by nonoperative means.[1, 2] The success of the Smith technique lay essentially in the ability of the operator, under fluoroscopic control, to move the tip of the tube, even in the presence of distention, through the pylorus and well into the duodenum with dispatch. However, to achieve a steady and progressive descent of the tube from that point into the lower reaches of the distended bowel is another matter.

The present effort was directed initially at devising a technique which would permit the nonoperative introduction of a long intestinal tube, in patients with distention into the upper reaches of the jejunum, followed by steady downward migration of the tube. Achievement of this objective, it was believed, would be most readily attained by use of an obturator within the tube, which could be withdrawn easily on completion of the descent. Our efforts to secure such ready passage of a long tube throughout the small bowel, without recourse to operation in patients with distention, have not been rewarded with the measure of success we had anticipated. Nevertheless, as some of our case reports suggest, the struggle to achieve nonoperative decompression quickly by intubation has by no means been all failure.* Yet, the special virtue of the method described would appear to lie in its use as an operative aid to the surgeon in achieving quick decompression of the distended intestine with-

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*We are proposing to explore the thesis of dividing the distal Einhorn-like bucket into 2 fragments, pivoting the distal on the proximal segment. If a rocking motion can be imparted to the distal segment by a gentle current, the failure rate in getting the tube to descend without operation may be lessened.

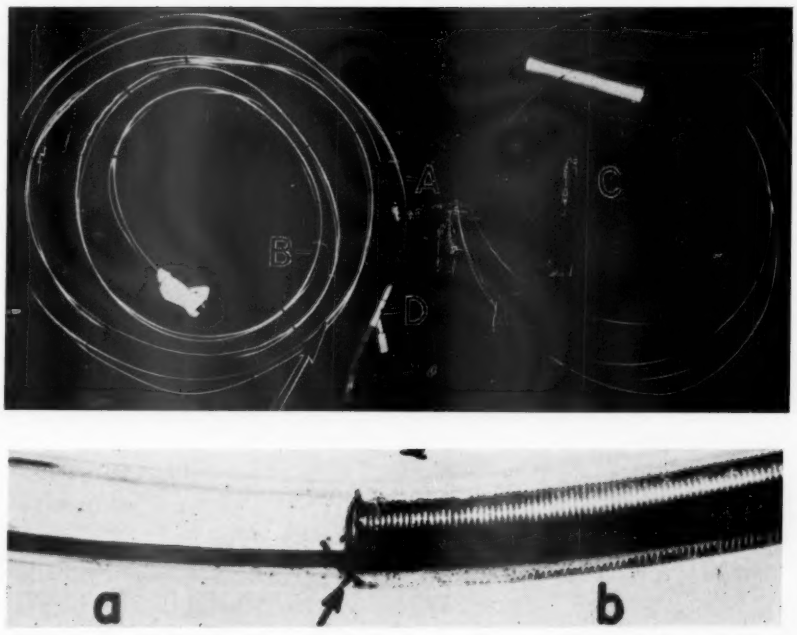


Fig. 1. Photograph of the long intestinal tube. *A,* The proximal 2 feet, without the coiled spring, are arranged to provide comfort for nose and oropharynx. *B,* The terminal 8 feet of the long intestinal tube which contains the coiled spring for overcoming frictional force upon withdrawal of the music-wire stylet. *C,* The music-wire stylet (No. 17, 0.039 mm.) with handle. *D,* The Y connector to provide a source for suction and for removal of stylet. The arrows indicate the junction of the soft portion *(a)* and the coiled spring *(b)*.

out recourse to enterotomy or enterostomy.

In part, the success of this technique in achieving quick passage of the tube through long reaches of distended intestine at operation rests upon the insertion of a coiled spring within the tube. The coiled spring assures preservation of gentle and well-rounded curves in the tube while it is positioned within the intestinal coils, and thus completely eliminates any difficulty in the withdrawal of the obturator. Our experience shows that surgeons may find this tube quite useful in their operative attack upon the distended and obstructed bowel.

Apart from employment of an internal flexible obturator, which permits rapid advancement of the tube through long lengths of distended intestine, and use of a coiled internal spring within the tube, which eliminates friction and assures easy withdrawal of the obturator, other considerations of some importance in the design of the tube are features already available in other tubes. These are (1) a small balloon at the end of the tube which, when the intestine is distended, will encourage its descent, (2) size of lumen adequate for suction, (3) tubing which provides minimal irritation to the nasal passages and oropharynx, and (4) adequate length for intubation of the entire small intestine.

DETAILS OF DESIGN OF THE TUBE

With the aid of Mr. John A. Phelan, who has been very helpful in designing many instruments for use in this hospital over the past quarter of a century, a tube has been developed which can be passed rapidly through the entire intestinal tract to the ileocecal valve (Figs. 1, 2, and 3). The tube is made of polyvinyl plastic (Goodrich chemical Geon—vinyl resin Geon compound No. 8854, transparent). Resilience and flexibility of the assembled tube are achieved by use of a No. 17 music-wire stylet (diameter 0.039 inch or 0.0975 mm.) that extends the

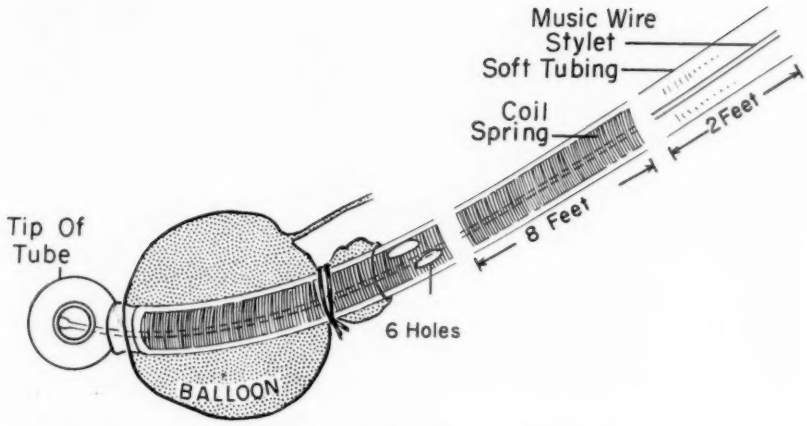


Fig. 2. Schematic illustration of the 3 essential components of the long intestinal tube.

entire length of the tube. Friction and binding which ordinarily would preclude withdrawal of the obturator, are eliminated by use of a coiled spring of stainless steel (0.014 inch in diameter) within the plastic tube lumen.[1] The tube is 10 feet in length. The distal 8 feet of the tube contain the coiled spring; in the more proximal portion, the spring is eliminated so that only the soft tubing remains in the nose and oral pharynx of the patient on completion of the intubation.[2, 3] The internal diameter of the tube is $\frac{3}{16}$ inch (4.7 mm.) and the outer diameter is $\frac{1}{4}$ inch (6.3 mm.). The wall thickness is $\frac{1}{32}$ inch (0.8 mm.). The large internal diameter assures a lumen efficient for suction. A rubber balloon of 15 ml. capacity surrounds the distal tip of the tube, affording the surgeon an added device to exert traction upon the tube if necessary. It also precludes penetration or perforation of the bowel by the advancing tube. The tip consists of a rounded metal ball with a lumen opening of $\frac{9}{32}$ inch (7.5 mm.) for maximal suction. In addition, there are 6 holes for suction proximal to the balloon. Opacity to roentgen rays is provided by the steel coil. A Y connection on the proximal end of the tube allows suction to be applied during its passage. Simplicity of design makes possible inexpensive production.*

*Phelan Manufacturing Co., 2523 Minnehaha Avenue, Minneapolis 4, Minn.

TECHNIQUE OF INTUBATION

Any inlying nasogastric tube in the stomach is removed. The long music-wire stylet is introduced into the entire tube through the Y connector. The distal portion of the tube is lubricated externally with KY or petroleum jelly. The inner surface of the tube is lubricated by injection of 30 to 60 ml. of mineral oil into its proximal orifice. The tube is then introduced through the mouth and is passed into the stomach. The surgeon inserts his hand toward the attic of the abdomen to receive and guide the tube through the pylorus as it is advanced by the intubator, who stands beside the anesthetist. As the tube advances, the surgeon follows its steady movement to the duodenojejunal angle. Suction is applied to evacuate the distended intestine as the tube advances. Ordinarily the tube can be advanced easily with little manipulation of the distended bowel. Mere elevation of succeeding loops of distended intestinal coils usually suffices to permit an almost uninterrupted descent of the tube. Occasionally, progress has to be aided by some manipulation of the distended intestinal coils just proximal to the advancing tube. After the tube has been inserted as far as desired, the stylet is removed. One hand is placed on the coiled portion of the tube and the other hand on the handle attached to the wire stylet and it is simply pulled out of the tube. This

will then leave the entire tube completely flaccid and malleable. The Y connector is then removed. The end of the long tube is fastened to the tip of a nasogastric tube which has been passed through the nose and recovered in the oropharynx. In this manner the soft portion of the intestinal tube is brought out through the nose. The tube is advanced until the coiled spring is in the midesophagus, well beyond the oropharynx.[3] The balloon is then deflated. The obstructing mechanism is managed as the situation dictates. Before the operation is completed, an indwelling nasogastric tube is passed into the stomach through the patient's other nostril. A soft No. 16 Fr. nonirritating tube is used which has been placed on ice cubes for a few minutes to insure enough stiffness to enable the anesthetist to pass it easily.

The tube remains in place in the postoperative period until assurances of physiologic continuity have been noted and until the patient can accept oral intake of food without intestinal colic. Our practice has been to leave such tubes 3 to 7 days after operation, depending upon circumstances. The tube is then cleansed by washing and irrigation, the wire stylet and the Y connector are replaced, and the tube is again ready for use. The tube is sterilized by immersion in an aqueous Zephiran solution (1 to 1000) over a 24-hour period, followed by a half hour soak in 95 per cent alcohol.

EXPERIENCE WITH THE LONG INTESTINAL TUBE AT OPERATION

In 21 patients, intestinal intubation has been carried out at operation. The tube was successfully passed without difficulty in 18 patients. In 3 instances, because of some difficulty in advancing the tube, we did not persist in our efforts at intubation. In 1 patient, the duodenojejunal angle could not be identified because of the presence of several adherent loops in this area, a circumstance which made control of the tip difficult. In another instance, the abdominal incision was so low that the surgeon desisted in attempting to guide advancement of the tube rather than extending the incision. In an early case, before a balloon and a rounded tip were used routinely, perforation of the duodenum occurred because the operating surgeon failed to follow the advance of the tube as it was being propelled forward by the intubator. The opening was closed, the adhesive obstruction was repaired, and the patient came to no serious harm through the misadventure.

Of the 18 patients successfully treated, adequate decompression was achieved in all, both at operation and in the postoperative period. The inlying duodenal tube introduced just before the conclusion of the operation was removed usually in 48 to 72 hours. Prior to extubation through the mouth, the throat was sprayed with 5 per cent Cyclaine. Patients thereby experienced a minimal amount of discomfort in the oral pharynx on

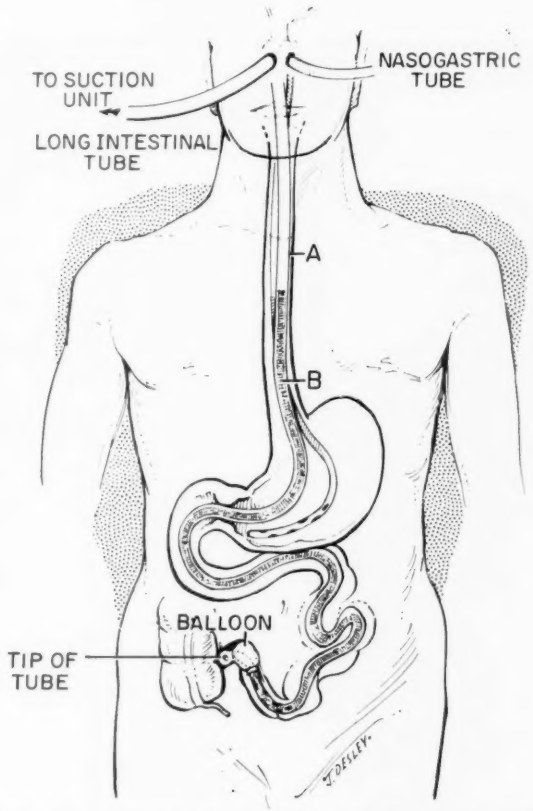


Fig. 3. Schematic drawing showing in situ position of the tube in the patient's nose, esophagus, and small intestine. The upper segment of the tube *(A)* lying in the nose and oropharynx has no coiled spring within it, as does the remainder of the long intestinal tube *(B)*.

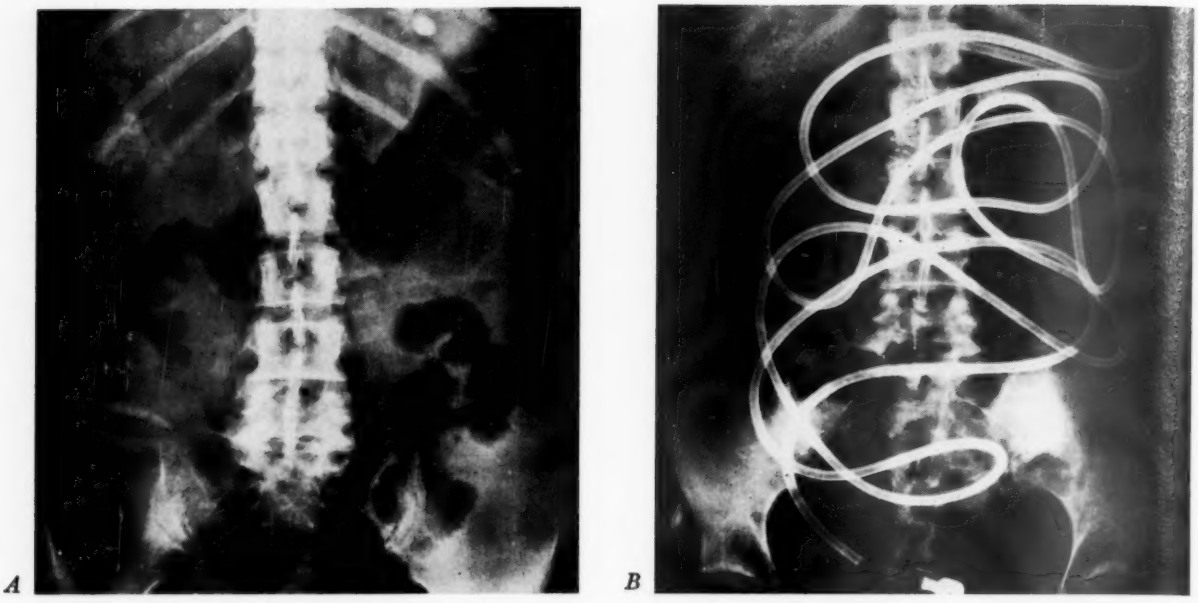


Fig. 4. Case 2. *A,* Scout film shows small bowel distention from partial obstruction. *B,* Film made immediately after operation shows long intestinal tube in place. Evidence of distention has disappeared.

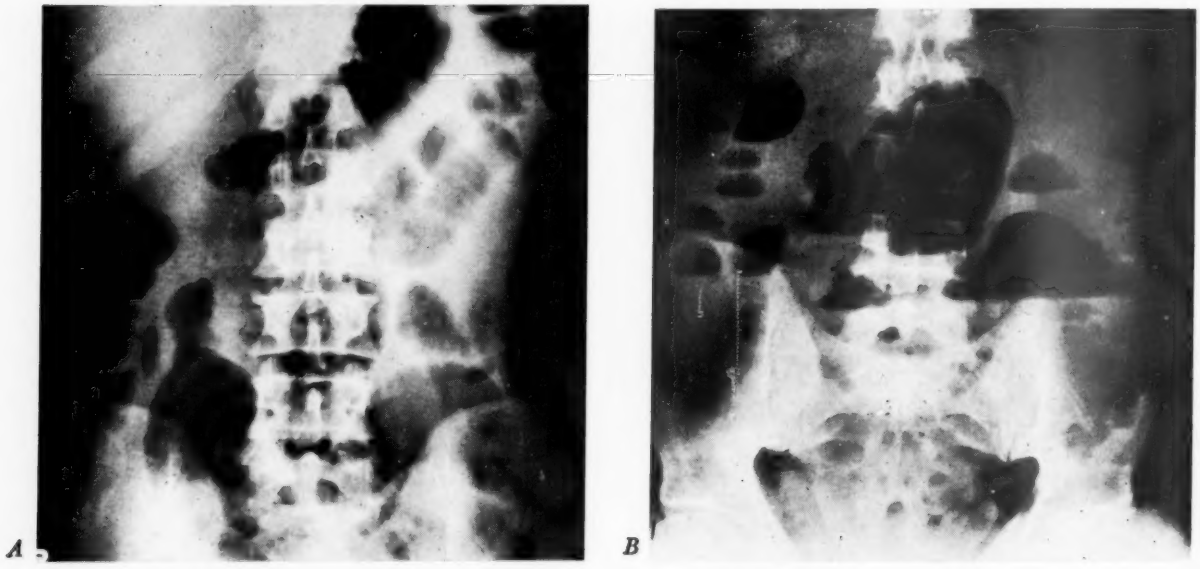


Fig. 5. Case 3. *A* and *B,* Scout films which show small bowel distention and a persistent loop of dilated bowel in right lower quadrant.

withdrawal of the tube. As was previously mentioned, the proximal 2 feet of the tube, lying within the nose and oropharynx, does not carry the coiled spring.

Discussion. Results attending use of the long intestinal tube have been very encouraging in the treatment of small bowel obstruction and a number of other acute abdominal states accompanied by intestinal distention.

The rapidity of intubation and decompression during operation aids the surgeon in the assessment of the mechanism of obstruction. It eliminates the necessity of enterotomy or enterostomy and allows decompression with minimal manipulation of

distended intestine. Patients appear to tolerate the soft tube in the nasal passages and oropharynx almost as well as the usual nasogastric tube. Inasmuch as the functional end of the tube occupies the lower reaches of the bowel, it is necessary, on completion of the operative procedure, to leave an indwelling duodenal tube in the stomach to assure satisfactory gastric decompression during the early days of postoperative convalescence.

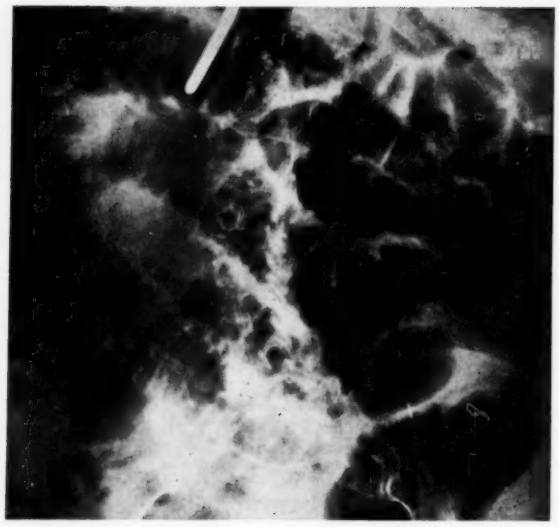
CASE REPORTS—OPERATIVE DECOMPRESSION

Case 1. M. K., a 27-year-old, 300-pound (136.3-kilogram) white female, was admitted on April 28, 1960, with a history of nausea, vomiting, and crampy abdominal pain of 2 days' duration. Incarceration of the sigmoid colon in an umbilical hernia in November, 1958, had necessitated exteriorization of the sigmoid colon, with establishment of a double-barrel colostomy. Physical examination on this admission showed a distended abdomen with a hernial defect containing multiple distended loops of bowel. Hyperactive bowel sounds were much in evidence. Roentgenograms showed several dilated loops of small intestine in the hernial defect. Passage of both the Smith tube and the one described herein was attempted under fluoroscopy, but without success. The patient then underwent operation. With the method described, decompression was readily achieved. The tube was passed to the site of obstruction in a few minutes. The obstructing mechanism was found to be an adhesive band which bound the ileum down in the right lower quadrant. The adhesion was divided. Simultaneous colectomy, with excision of the previous colostomy, and an end-to-end anastomosis were performed. The long tube was removed on the fifth day and the patient recovered uneventfully.

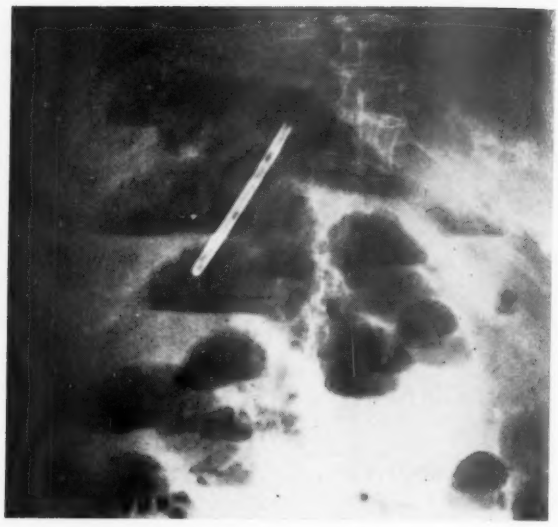
Case 2. A. N., a 39-year-old woman, had undergone a total colectomy for ulcerative colitis in December, 1959. She subsequently developed retraction of the ileostomy stoma with abscess and fistula formation. The fistula failed to close and repeated recurrent episodes of incomplete small bowel obstruction occurred. On admission Oct. 27, 1960, physical examination showed distention, moderate abdominal tenderness, and hyperactive bowel sounds. Many coils of distended small bowel were discernible on inspection of the roentgenograms (Fig. 4, *A*). At operation the long tube was passed with ease within 7 minutes and immediate decompression was effected (Fig. 4, *B*). The obstruction was found to be due to multiple adhesions. Fistulas in the midjejunum and distal ileum were resected and lysis of adhesions was carried out. The tube remained in place for 7 days, until it was evident the patient could accept oral feeding well. The patient's course was remarkably uncomplicated and she was discharged in satisfactory condition on the twenty-third postoperative day.

Case 3. T. B., a 60-year-old man, was admitted Nov. 29, 1960, with a 1-week history of epigastric pain accompanied by nausea, emesis, progressive obstipation, and fever. His treatment prior to admission had been focused on antibiotics. Physical examination showed a tender and distended abdomen with absent bowel sounds and a tender, boggy mass in the pelvis. Abdominal scout films showed a partial small bowel obstruction with a persistently dilated small bowel loop in the right lower quadrant (Fig. 5, *A* and *B*). Exploratory operation was performed and the long tube was easily passed in less than 10 minutes, with immediate and complete decompression of the small bowel up to the site of obstruction (Fig. 6). The terminal ileum was found to be involved in an inflammatory mass which had resulted from a ruptured appendix. Extubation was carried out on the ninth postoperative day after demonstration of satisfactory acceptance of oral feeding. The patient had a protracted and slow recovery from the peritonitis and infection, but was discharged in good condition on the twenty-ninth day of his hospital stay.

Fig. 6. Case 3. Film taken immediately after operation which shows decompression achieved with tube without recourse to enterotomy or enterostomy.



A



B

Fig. 7. Case 4. Scout films which show extent of distention *(A)* and gas and fluid levels *(B)*. *C,* Film taken 12 hours after nonoperative decompression under fluoroscopy which shows ad-

Case 4. A. O., a 75-year-old woman who was known to have a stage III squamous-cell cancer of the cervix, had been treated on the gynecological service of this hospital in January, 1960. External irradiation had been carried out, followed by total hysterectomy. In November, 1960, she returned for radium therapy because of a vaginal recurrence. Signs of intestinal obstruction supervened, evidenced by the occurrence of crampy abdominal pain and distention (Fig. 7, *A* and *B*). Several masses could be felt on rectal examination. A long intestinal tube was passed under fluoroscopy within 15 minutes and decompression was successfully completed at 12 hours (Fig. 7, *C*). After 4 days, the tube was removed and the patient resumed oral alimentation. However, she soon demonstrated recurrent obstruction with increasing abdominal tenderness and elevation of the white blood cell count. Exploration was carried out and the bowel was decompressed at operation by passage of the long tube, which descended quickly to the midileum (Fig. 7, *D*).

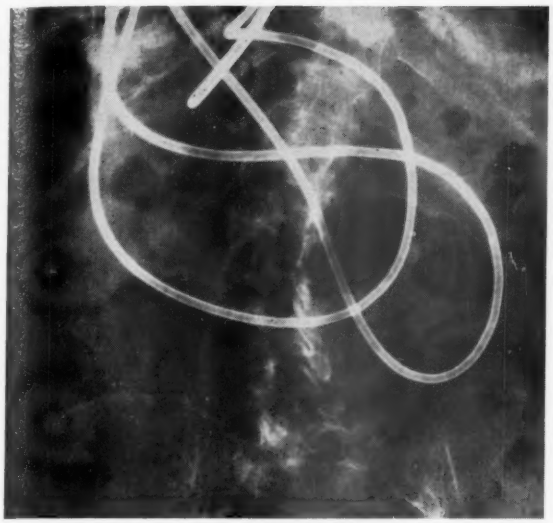
The obstructing carcinomatous mass at the terminal ileum was bypassed by performance of an ileotransverse colostomy. The long tube remained in place for 6 days and the patient was discharged on the eleventh postoperative day.

NONOPERATIVE DECOMPRESSION

There were 14 trials of nonoperative intubation with the tube passed under fluoroscopic visualization. In 8 patients passage of the tube 1 to 2 feet or more past the duodenojejunal angle (ligament of Treitz) was achieved. In 1 case the patient pulled his tube out after successful intubation. A second attempt failed and surgical intervention was required for decompression. Four patients required no further therapy. The case record of one of these is reported. Three patients required surgical intervention despite successful nonoperative intubation well into the upper jejunum. Persistence of distention suggested the necessity for operation. In each instance the operating surgeon remarked that the preoperative decompression had made the operative task surprisingly easy. The 6 patients in whom nonoperative passage of the tube failed were submitted to operation without delay. In these patients, the surgeon was able with the aid of the intubator to guide the tube down to the site of obstruction.

CASE REPORT—NONOPERATIVE DECOMPRESSION

Case 5. K. C., a 70-year-old woman, was known to have carcinoma of the right Fallopian tube with multiple intra-abdominal metastases proved at exploratory operation in January, 1960. She had been under treatment with Methotrexate. On admission, she gave a history of 2 days of intermittent, crampy abdominal distress, obstipation, distention, and emesis. Over the past



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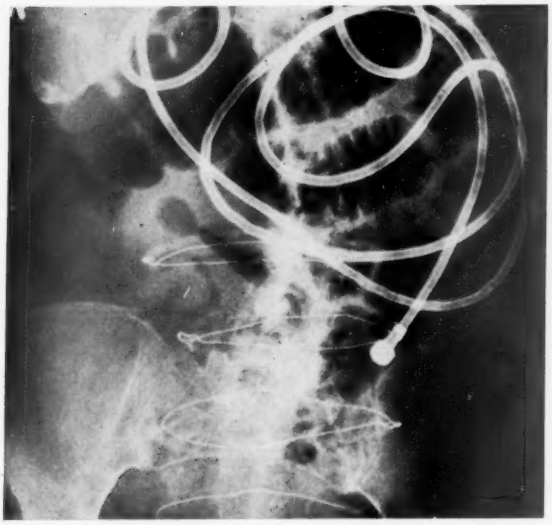

D

vance of the tube and minimal persistent distention. ***D,*** Postoperative film taken at 24 hours shows long intestinal tube in place and relief of distention. Wire retention sutures also are shown.

3 months, similar mild episodes had relented spontaneously. Roentgenograms showed several dilated loops of small intestine (Fig. 8, *A* and *B*). The long intestinal tube was passed under fluoroscopy to a point approximately 18 inches past the duodenojejunal angle (Fig. 8, *C*). Rapid decompression ensued with relief of distention within 12 hours (Fig. 8, *D*). The tube had passed meanwhile to the lower ileum. Within 24 hours the patient's obstruction had relented completely as evidenced by spontaneous bowel movements. After oral alimentation for 5 days with the tube in place and without incident, the tube was removed and the patient was discharged on the seventh day after intubation.

EFFORTS TO ENCOURAGE PASSING OF INLYING LONG INTESTINAL TUBES

The major difficulty of urging an inlying long intestinal tube to descend into the more distal distended intestinal coils lies in the problem of the drag on the tube. In other words, the observed inertia of the tube is to be attributed primarily to the circumstance that, despite contraction of the intestine upon the balloon, the drag of the tube around the intestinal coils nullifies any forward propulsion exerted upon the balloon by the contractile activity of the distended bowel. In dogs, we have placed electrodes upon opposite sides of an inlying tube near the balloon, connected to a Gras stimulator. Twenty to 30 stimulations per minute at varying voltages, as high as 400 v., have been applied to the electrodes, but without material effect upon accelerating the descent of the tube. Obvious evidence of contraction of the bowel wall was always noted in dogs, with the abdomen open, on the application of higher voltage stimulation. Moreover, voltages in the range of 300 to 400 v. obviously are hazardous for the intestinal mucosa. Mineral oil and solutions of magnesium sulfate, varying in concentration from 5 to 50 per cent, have been injected in attempts to augment the rapidity of descent of a balloon-tipped tube, but without any real evidence of success. These unsuccessful efforts antedated the innovation of the stylet and use of a tube with a coiled spring. It may well be that solutions such as magnesium sulfate used in conjunction with the tube described may augment the rate of descent and thereby enhance the utility of this method in achieving decompression by nonoperative means. We are proposing to examine this possibility further.

SUMMARY AND CONCLUSION

A long intestinal tube has been devised for rapid intubation of the distended small

intestine. Although this effort began as an attempt to achieve decompression by nonoperative means, the most important use of the method has proved to be in effecting ready decompression of the distended and obstructed small bowel at operation without

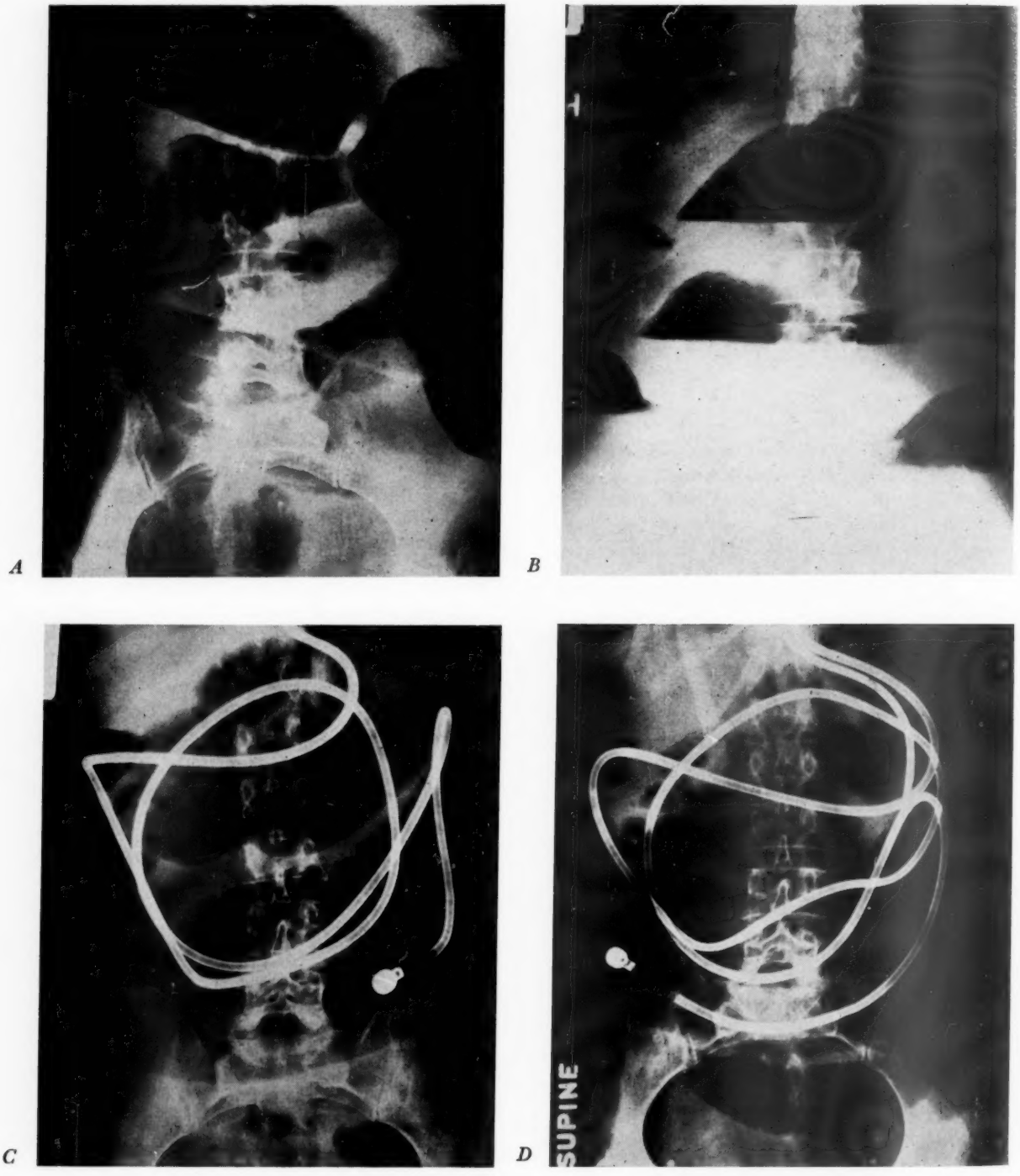

Fig. 8. Case 5. *A* and *B*, Scout films which show small bowel dilatation with air and fluid levels. *C*, Film taken directly after nonoperative intubation under fluoroscopy which shows that the tube was passed to a point more than 18 inches beyond the duodenojejunal angle. *D*, Film taken 12 hours after nonoperative decompression which shows the advance of the long intestinal tube well into the midileum with complete decompression.

recourse to enterotomy or enterostomy. Forces of friction have been overcome by a thin music-wire stylet and placement of a coiled spring within the tube. The coiled spring has made it possible to secure ready passage of the tube into the distended intestinal coils, as well as to insure easy withdrawal of the stylet when the descent of the tube is complete.

It may yet be possible to increase the usefulness of the method as a nonoperative technique of achieving decompression by the use of agents which enhance intestinal contractility and thereby encourage descent of the tube.

Both the operative and nonoperative techniques of using the method are described. Case reports which illustrate the use of the method with and without recourse to operation are included. It is believed that this method may come to serve surgeons usefully in their attack upon bowel obstruction.

ADDENDUM

As of Feb. 16, 1961, 4 additional patients with intestinal obstruction have undergone operative decompression by the method described. In each instance the intestinal tube was passed successfully to the distal ileum with minimal manipulation and immediate decompression was achieved. No intubation required more than 10 minutes and none of the patients complained of the presence of the tube in the nasopharynx postoperatively.

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Influence of 5-fluorouracil on wound healing

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Cytotoxic agents and antimetabolites are used in current surgical practice to inhibit the implantation and dissemination of neoplastic cells. Such therapy may ultimately be shown to benefit a limited number of cancer patients. Since extensive clinical trials are now in progress,[8] a knowledge of the harmful effects of these substances is important. This paper reports experimental evidence which demonstrates that one of these chemicals, 5-fluorouracil, interferes with the normal process of abdominal wound healing.

Alkylating agents and antimetabolites have toxic effects which may be accentuated by surgical trauma. Morales and McDonald[6] and Wolberg and Curreri[10] demonstrated such an effect in animals. If these agents are capable of inhibiting the growth of neoplastic tissue, they may interfere also with the proliferating tissue of repair. Farhat and associates[3, 4] noted a decrease in the tensile strength of experimental abdominal wounds after administration of nitrogen mustard, but not after thio TEPA had been given. The latter was confirmed by Rath and Enquist.[7] Conn and associates,[2] studying gastrotomy wounds in dogs, noted no difference in healing in control animals as compared with healing in those treated with nitrogen mustard or thio TEPA. Krementz and associates[5] found that triethylenemelamine caused a significant depression in healing of gastric wounds in guinea pigs.

During the past three years considerable enthusiasm has been engendered by the synthesis and laboratory and clinical testing of the fluorinated pyrimidines. This group of compounds, of which 5-fluorouracil has been most intensively studied, has a definite effect on the natural history of many neoplasms.[1] It is of surgical significance that cancer of the breast and colon are high on the list of tumors influenced by this agent. 5-Fluorouracil might be of value as an anticancer agent given at the time of operation to patients who are operated upon for these two neoplasms, although it may be too toxic to use in full dosage in the postoperative patient.

The fluorinated pyrimidines act as antimetabolites by interfering with the synthesis of certain nucleic acids which are essential to cell division. Our interest in the effect of 5-fluorouracil on wound healing was stimulated by a patient who developed intestinal obstruction 3 days after the completion of a 5-day course of 5-fluorouracil for a nonresectable cancer of the rectum.[9] Though no gross evidence of interference with wound healing was noted, it was decided to pursue the problem in the laboratory.

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METHODS

Actively growing male Sprague-Dawley rats which weighed 100 to 125 grams were utilized. Ether anesthesia was used and sterile conditions were maintained. A midline incision, 5 cm. in length, was made in the anterior abdominal wall and carried through the peritoneum. The abdominal wound was closed with a continuous suture of No. 4-0 silk through all layers except the skin, which was closed separately. On the seventh postoperative day, the skin of the abdomen was excised and the suture in the abdominal wall was gently removed. A 4 by 5 cm. full-thickness block of the abdominal wall was excised and clips were attached at either side as indicated in Fig. 1. One clip was suspended from a ring stand; a distensible rubber vessel was attached to the second clip and filled with water at a constant rate (approximately 250 ml. per minute). When the incision separated, the bag fell, providing a sharp end point. This method was used by Farhat and associates.

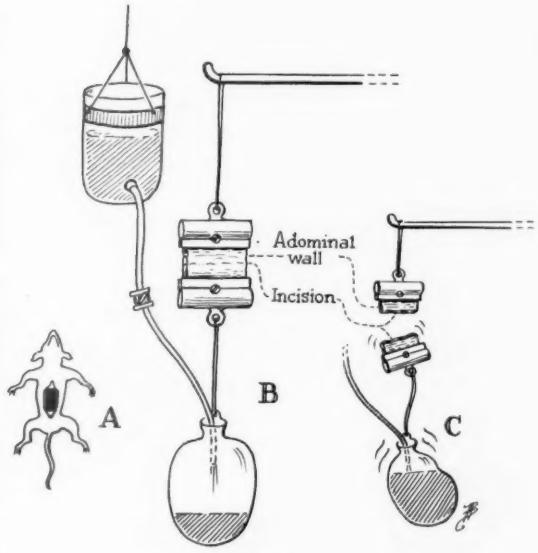

Fig. 1

Preliminary studies showed that 5-fluorouracil prevents normal weight gain of growing rats. In order to eliminate nutrition as a factor in decreased tensile strength, 4 experimental groups were established. Group I animals served as controls. They were subjected to the same surgical procedure but were maintained on an ad libitum diet and were not given the chemical. Group II animals were maintained on limited rations to prevent weight gain without producing weight loss. 5-Fluorouracil was administered to the animals in Group III and Group IV, but the animals in Group IV were also maintained on limited rations while Group III animals were fed ad libitum. Each group consisted of 25 to 30 animals.

All animals were weighed before and after the experiment. 5-Fluorouracil, 75 mg. per kilogram, was administered intramuscularly in 2 doses, the first immediately after operation and the second on the following day. The total dose was comparable (milligrams per kilogram) to the average dose given to human beings, but it was given in 2 days rather than 5 days in order to simulate the dosage scheme of other drugs now used in adjuvant cancer chemotherapy studies.

RESULTS

The average weight change in the 4 experimental groups is presented in Table I. Although weight gain was more pronounced in the control group (I), an increase in weight also occurred in the treated animals (III). Insignificant weight loss occurred in the inadequately fed rats in which the diet was adjusted in order to prevent weight gain (II). A significant loss occurred in the treated group maintained on the same diet (IV). It is apparent that 5-fluorouracil interfered with the nutritional status of the animals.

Table I. *Weight change in the 4 experimental groups*

	Group I (control)	*Group II (limited rations)*	*Group III (5-fluorouracil)*	*Group IV (limited rations + 5-fluorouracil)*
Average weight change (grams)	+41	−3	+25	−23

Table II. *Tension necessary to produce wound separation*

	Group I (control)	*Group II (limited rations)*	*Group III (5-fluorouracil)*	*Group IV (limited rations + 5-fluorouracil)*
No. of animals	25	27	28	31
Mean force (Gm.)	664	582	538	338
Standard deviation	±190	±188	±195	±158

The force necessary to produce separation of the abdominal incision was measured 7 days after the initial operation. The results are presented in Table II.

A greater force was necessary to produce separation of the wound in the control group than in any of the others. Wound strength was somewhat diminished in the animals that had not gained weight, but this difference was not statistically significant ($P = > 0.05$). A greater decrease in wound strength was noted in both groups which received 5-fluorouracil, especially in animals which were also maintained on an inadequate diet. Spontaneous wound separation did not occur in any animal.

A statistical comparison of the results obtained in the various experimental groups is presented in Table III. The difference in wound strength of Groups I and II is not statistically significant; thus the failure to gain weight does not in itself significantly influence wound healing as measured in these experiments.

However, the difference between Groups I and III is statistically significant, indicating that 5-fluorouracil does influence adversely the reparative process in the experimental wound. Although the finding is not statistically significant, wound healing was less adequate in the animals which received 5-fluorouracil than in those on limited rations, despite the fact that significant weight gain occurred in the former while weight loss occurred in the latter. Moreover, the difference between Groups II and IV is highly significant ($P < 0.01$), indicating that the addition of 5-fluorouracil when the nutritional status is less than optimal adversely influences wound strength, whereas the nutritional state, per se, does not. There is also a significant difference between Groups III and IV, which suggests that an inadequate dietary intake exaggerates the healing deficiency produced by 5-fluorouracil.

Table III. *Statistical comparison of experimental groups*

Groups	*t*	*P*
I and II	1.575	> 0.05
I and III	2.390	< 0.05
I and IV	5.730	< 0.01
II and III	0.854	> 0.05
II and IV	4.440	< 0.01
III and IV	3.60	< 0.01

CONCLUSIONS

5-Fluorouracil caused decrease in the tensile strength of a standard wound in the abdominal wall of rats maintained on optimal food intake.

When diet was restricted, 5-fluorouracil caused impairment of wound healing greater than that observed in animals given the restricted diet only.

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The effect of early eschar excision upon the nutritional state and rate of wound closure of rats with full-thickness thermal burns

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Early excision of the eschar from areas of full-thickness burn combined with immediate skin grafting of the areas has been demonstrated to shorten the period of hospitalization and convalescence for patients with full-thickness burns covering between 20 and 35 per cent of body surface area. The clinical trial of this form of treatment has been limited to young patients, usually with less than 35 per cent of body surface area burned full thickness.[6, 7]

Recent literature relating to the treatment of burns has been concerned with the role of the eschar in cases of severe infection and with the proper time and method of eschar removal.[6-8] It is not known whether the eschar serves any useful purpose other than that of a temporary dressing. This study is an investigation of the effect of early eschar excision upon the nutritional state and rate of wound closure of rats with full-thickness burns.

METHODS AND MATERIALS

Thirty Holtzman strain male Sprague-Dawley albino rats were used in the experiments. All animals were the same age with an original mean weight of 236 grams, with a standard deviation of 12 grams. The animals were housed in individual cages in an animal room with the ambient temperature maintained at 20 ± 1° C. and the relative humidity ranging between 50 and 70 per cent.

The 30 animals were assigned at random to 4 experimental groups, (1) full-thickness burn group (B group) of 10 animals, (2) full-thickness burn group composed of 10 animals with eschars excised on the fifth postburn day (B-E group), (3) skin excision group (SE group) made up of 6 animals, and (4) control group (C group) composed of 4 animals.

All animals were offered a diet of Purina laboratory chow and given tap water ad libitum. Food intake was measured daily to the nearest gram. At intervals of 5 to 9 days the animals were fasted for from 12 to 14 hours and then weighed to the nearest gram. All wounds were measured by the method of Carrel[3] immediately after the weighing of the animals.

After a 16-day acclimation period the hair was clipped from the entire back of all animals, and the wounds were then produced in the B, B-E, and SE groups. Group B and B-E animals were burned by immersion for 30 seconds in water at 90° C. This produced full-thickness burns of the back with a mean size of 25 ± 2 per cent of body surface area in the B group and 24 ± 2 per cent of body surface area in the B-E group. On the same day animals in the SE group had the skin of the back excised with

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a template used as a guide. The mean area of skin excised was 49 ± 3 cm.^{2}, which produced wounds of a mean size of 18 ± 1.7 per cent of the body surface area. Both experimental and control animals received 100 to 120 seconds of ether anesthesia and were given lactate Ringer's solution intraperitoneally amounting to 10 per cent of body weight. On the fifth postinjury day, when the eschars were clearly demarcated, animals in the B-E group were again anesthetized with ether and their eschars excised, with a 2 to 5 mm. rim of eschar left at the junction of eschar and uninjured skin.

Food intake was measured daily, and animal weight and wound size were measured weekly through the seventy-sixth postinjury day. On the first, twelfth, and twenty-ninth days, skin, rectal, and, when present, wound temperatures were obtained for all animals by means of a telethermometer with cutaneous and internal probes. Once each week the hair was clipped from the entire back of the control animals and from around the wounds of the injured animals.

No animals died or were sacrificed from the B, SE, and C groups during this study. One animal from the B-E group died on the eighth postinjury day but autopsy did not demonstrate the cause of death. In addition, 1 animal was eliminated from the B-E group because of chronic renal disease discovered at the termination of the study. Thus, in the analysis of the data there were 8 animals in the B-E group. Autopsy examination of all other animals at the termination of the experiment demonstrated no significant findings other than those related to the wounds.

During this 76-day period differences between mean values for the parameters measured were tested for statistical significance by means of the t test. The null hypothesis was rejected at the 0.05 level of probability.

RESULTS

Food intake. The food consumption data for all groups for the entire experiment are summarized in Table I. Mean values for food intake represent grams of food consumed per animal per day. In the calculation of these values, data collected on fast days and on the first postfasting days were eliminated. Thus food intake as measured represents the mean quantity per animal per day for 4 to 6 consecutive days.

The food intake for the C group was very stable, ranging between 29 and 31 grams per animal per day throughout the study. The SE and B-E groups reacted similarly in food consumption, showing an immediate and prolonged increase above the food consumption of both B and C groups. The first 10 postinjury days, during which the B-E group consumed significantly less food

Table I. *Mean daily food intake for control (C), burn (B), burn-excision (B-E), and skin excision (SE) groups for all time periods*

Days postinjury	C (4 rats)		B (10 rats)		B-E (8 rats)		SE (6 rats)	
	Mean*	Standard deviation	Mean*	Standard deviation	Mean*	Standard deviation	Mean*	Standard deviation
1- 4	31	2.0	28†	2.0	30	3.0	41†	4.0
5-10	31	1.7	30	3.7	33†	4.7	39†	2.4
11-17	30	1.0	31	2.1	34†	1.5	35†	2.6
18-24	29	1.3	31	2.1	34†	1.9	35†	1.7
25-31	30	1.3	33	2.3	36†	2.2	36†	2.8
32-39	29	1.7	34†	2.8	37†	2.3	35†	2.1
40-47	29	1.7	33†	2.2	35†	2.7	33†	2.4
48-55	30	2.1	33†	1.8	33	4.1	33	2.3
56-62	31	1.7	35	3.0	34†	1.7	33	3.4
63-69	31	3.0	33	2.5	32	4.1	34	4.3
70-76	29	2.1	32	3.0	32†	2.1	32	3.7

*Mean represents grams of food consumed per animal.
†Difference between this figure and corresponding mean of control group significant at 0.05 or beyond.

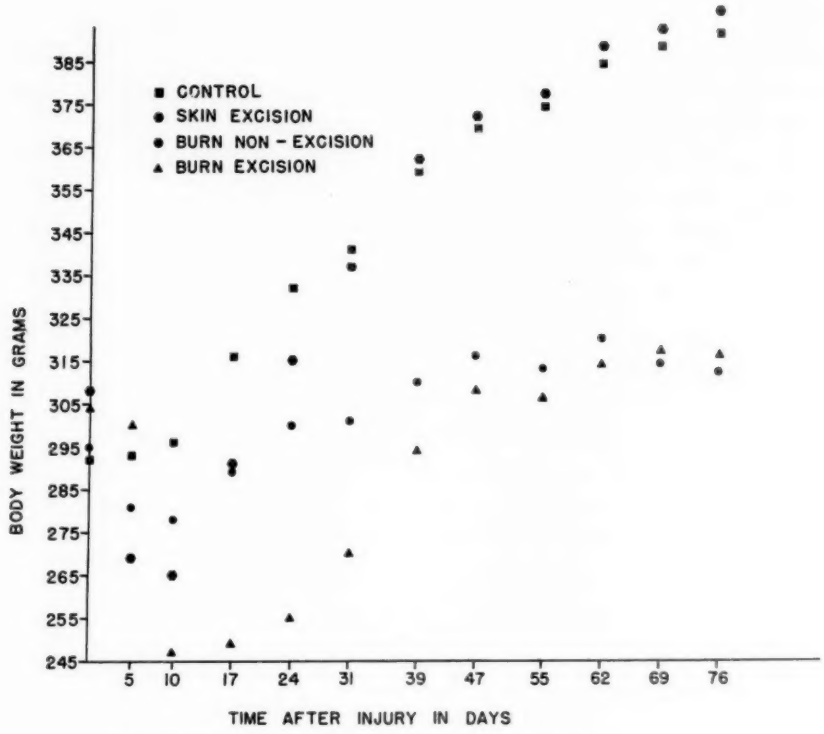

Fig. 1. Changes in mean body weight after injury.

than the SE group, include 4 days during which the eschars of the B-E group were intact plus the period of eschar excision with its attendant trauma which was experienced by no other group. This probably accounts for the significantly lower food intake for the B-E group as compared to the SE group during this 10-day period.

Food intake for the B group is quite different from that of the SE and B-E groups. Not until the thirty-second day period did the B group consume significantly more food than the C group, and then the increment persisted for only 3 weeks to the forty-eighth to fifty-fifth day period. This period of increased food consumption by the B group corresponds to the time period during which the eschars of B group became loose and spontaneously separated. During the first 31 days, while most of the B group had intact eschars, their food intake was no different from that of the C group and was significantly less than the food intake of both the SE and B-E groups. These data suggest that the presence of intact eschars in the animals of B group significantly lowered their food requirement in comparison to that of the SE and B-E groups.

Weight changes. The mean weights for all groups for the entire experiment are presented in Table II and Fig. 1. Immediately before injury there was no significant difference in the mean weights of the 4 groups. To minimize the effect of tissue excision upon the weights for the SE and B-E groups, the mean weights of excised skin or eschars were added to the group mean weights of the SE and B-E groups through the seventeenth postinjury day. From the tenth to seventeenth day on, differences between the B and B-E groups and the C group were significant. Differences between the SE group and the C group were not significant during any time period.

Table III shows the calculated mean daily weight change for the 4 groups for each measurement period. The B-E group lost the most weight at the most rapid rate. The SE group was second in total amount and rapidity of weight loss. Both total amount and

rate of weight loss are significantly less for the B group than for the SE and B-E groups.

Between the eleventh and seventeenth postinjury days all 3 groups of injured animals began to gain weight. However, the difference in rate of weight gain is striking. The SE group far exceeded the B and B-E groups in rate of weight gain (P value < 0.02 for SE versus B-E through thirty-first postinjury day; P value < 0.01 for SE versus B through thirty-ninth postinjury day). During the twenty-fifth to thirty-first postinjury day period the SE group actually exceeded the C group in rate of daily weight gain. As a result of the rapid rate of weight gain for the SE group, its curve for mean weight (Fig. 1) is almost superimposed upon the curve for the C group from the thirty-first postinjury day.

The B-E group showed the longest time lapse before reaching its maximum rate of weight gain. Between the twenty-fifth and forty-seventh postinjury days the B-E group consistently gained weight at a significantly faster rate than the B group (P value < 0.05 for all comparisons). However, the B-E group never significantly surpassed either the SE or C groups in rate of weight gain.

The B group never demonstrated a rate of weight gain comparable to that of either the SE or B-E group. The total weight loss

Table II. *Mean body weights for control and experimental groups for the entire experiment*

	Control		*Burn*		*Burn-excision*		*Skin excision*	
Days postinjury	*Mean**	*Standard deviation*	*Mean**	*Standard deviation*	*Mean**	*Standard deviation*	*Mean**	*Standard deviation*
0	292	6.3	295	15.3	304	15.3	308	23.1
5	293	2.8	281	15.4	300	15.6	296†	29.2
10	296	7.8	277	20.0	247‡§	21.3	266†	32.4
17	316	10.6	289§	22.0	249‡§	26.0	291†	34.9
24	332	14.8	300§	20.0	255§	29.3	315	42.0
31	341	13.5	301§	19.6	270§	35.9	337	42.0
39	359	15.3	310§	20.0	294§	34.9	362	49.7
47	369	17.1	316§	20.0	308§	34.1	372	49.7
55	374	14.4	313§	16.0	306§	40.0	377	47.1
62	384	14.5	320§	18.7	314§	37.3	388	50.8
69	388	17.5	314§	13.6	317§	47.2	392	53.8
76	391	17.1	312§	16.4	316§	51.3	396	55.0

*Mean body weight in grams.
†Ten grams added to mean weight representing the mean weight of excised skin.
‡Thirteen grams added to mean weight representing the mean weight of excised eschars.
§Difference between this figure and corresponding mean of control group significant at 0.05 or beyond.

Table III. *The mean rate of weight change in grams per day for all experimental groups during all time periods*

Days postinjury	*Control (4 rats)*	*Burn (10 rats)*	*Burn-excision (8 rats)*	*Skin excision (6 rats)*
0- 5	- .25	-3.50	- 1.00	-9.75
6-10	+ .75	-1.00	-13.25	- .75
11-17	+3.33	+2.00	+ .33	+4.17
18-24	+2.67	+1.83	+ 1.00	+4.00
25-31	+1.50	+ .17	+ 2.50	+4.16
32-39	+2.57	+1.28	+ 3.43	+3.57
40-47	+1.67	+1.00	+ 2.33	+1.67
48-55	+ .71	- .43	+ .28	+ .71
56-62	+1.67	+1.17	+ 1.33	+1.67
63-69	+ .67	-1.00	+ .50	+ .67
70-76	+ .50	- .67	- .17	+ .67

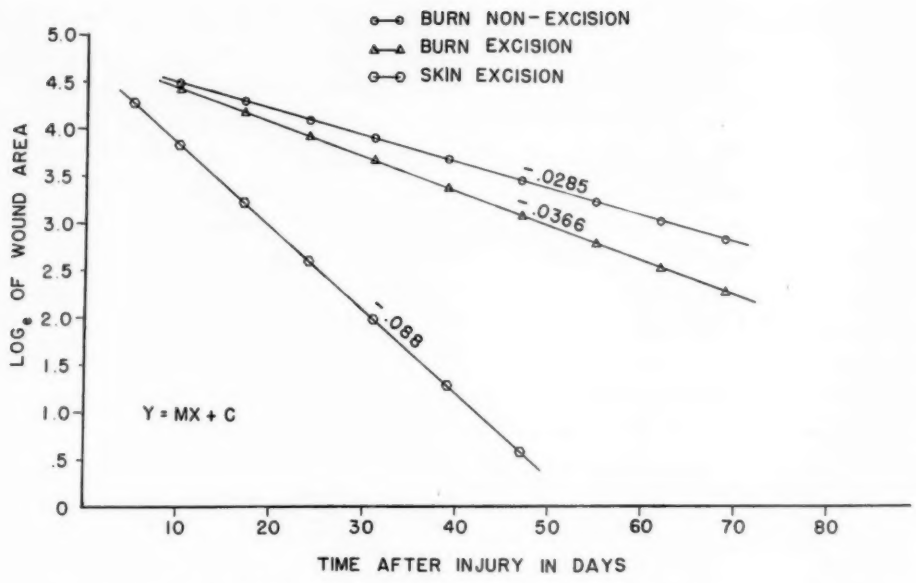

Fig. 2. The healing slopes and coefficients of regression for the 3 types of wounds produced. The formula of the straight line law for 2 quantities y and x is shown, when m = slope and c = y axis intercept.

and rate of weight gain of the B group are in sharp contrast to the weight responses of the SE and B-E groups, both of which lost significantly more weight but then gained at a more rapid rate than the B group.

Wound healing. A linear relationship exists between the natural logarithm of the area of unhealed wound and elapsed time since injury.[1] The slope of the resulting linear function can be calculated by the method of least squares. The resulting slope or regression coefficient represents the rate of wound healing. The correlation coefficient calculated for such a slope is a measure of the individual variance about the regression line. Comparison of the slopes can be performed by the method of Fisher.[4] Table IV gives the regression coefficients, correlation coefficients, and statistical comparison of the mean regression lines for wound healing of groups SE, B-E, and B. Fig. 2 shows a graphic comparison of regression lines of regression coefficients of the 3 injured groups.

The SE animals had a significantly faster rate of wound healing than did the B-E and B animals. The difference in rate of wound healing between B-E and B groups is also significant; the wounds of the B-E animals healed more rapidly. The difference in rate of wound healing for the SE and B-E groups may be due to damage of the wound bed of the latter animals at the time the burns were produced. Why eschar excision should significantly affect the rate of healing of full-thickness burns is less obvious, but analysis of the wounds at the termination of the experiment gave suggestive evidence.

Table V shows the original size of the wounds in the B-E and B animals, the proportion of the original wounds which healed by contraction, and the proportion which healed by epithelization. The portion of the original wounds of the B-E group which were eventually healed by epithelization is significantly greater than for the B group wounds. However, the portions of B-E and B group wounds healed by contraction are the same. This is indirect evidence that the difference in rate of wound healing between B-E and B groups is a result of a difference in the onset time or rate of epithelization and that the rate of contraction of a full-thickness burn wound is unaffected by eschar excision.

Although not shown in Table V, the per cent of the SE group wounds healed by epithelization was even smaller than the per

cent of B group wounds healed in that manner. Thus there is a true difference in the rate of contraction for an SE group wound when compared to either a B-E or a B group wound.

Temperature data. Lack of space precludes complete presentation of data on skin, wound, and rectal temperatures. However, two major summary points may be mentioned. First it should be noted that the ambient room temperature was 7 to 10° below the skin and wound temperatures of all animals. This eliminates the possibility that the animals could gain heat of vaporization from the environment for the water lost through the wounds. Second, although there were significant variations in skin and wound temperatures related to conservation and dissipation of heat, the internal temperatures of the injured animals were never significantly lower than those for the control animals.

DISCUSSION

The differences in nutritional response to the 3 types of trauma studied in this experiment are related to basic differences in the characteristics of the wounds. If one assumes that the basic nutritional requirement to achieve healing per unit of wound is the same for skin excision, burn-excision, and burn wounds, then one may look for obligatory nutritional requirements that are specifically related to the physical characteristics of the 3 types of wounds.

One line of reasoning which explains the results obtained in this experiment is that the extrarenal water loss from a skin excision wound is greater per unit of wound size by several fold than from a burn wound.[5] One would expect the extrarenal water loss from skin excision and burn-excision wounds to be comparable, although specific data on this point are not available.

At an ambient temperature of 20 ± 1° C. the animal sustaining such an increment in extrarenal water loss must furnish the heat of vaporization for such water.[2] As a direct result, the animal's obligatory heat loss increases and the obligatory heat production must also increase lest the animal's internal temperature fall.

Table IV. *The coefficients of regression, correlation coefficients, and statistical comparison of the healing slopes for the 3 injury groups*

Group	*Coefficient of regression*	*Correlation coefficient*	*Statistical comparisons of coefficients of regression*
Skin excision	−.0880	−.998	SE vs. B-E: $P < .001$; SE vs. B: $P < .001$
Burn-excision	−.0366	−.994	B-E vs. B: $P < .01$
Burn	−.0285	−.998	

Table V. *Comparison of burn-excision and burn wounds on the one hundredth postinjury day*

Group	*Original burn size (cm.²)*		*Remaining unhealed wound (cm.²)*		*Remaining wound plus area covered by epithelium (cm.²)*		*Area covered by epithelium (cm.²)*		*% of original wound covered by epithelium*	
	Mean	*Standard deviation*	*Mean*	*Standard deviation*	*Mean*	*Standard deviation*	*Mean*	*Standard deviation*	*Mean*	*Standard deviation*
Burn-excision	88	7.8	5.3	4.8	31.5	7.1	26.2	5.2	29.5	5.0
Burn	90	10.2	9.3	5.2	23.7	7.8	12.8	6.1	14.1	6.2
Difference	2		4.0		7.8		13.4		15.4	
P value	NS		NS		NS		<.001		<.001	

On the basis of this criterion the 3 types of wounds may be rated as to their capacity to increase the obligatory heat loss and thus increase the nutritional demands upon the injured animal. Skin excision and burn-excision wounds should be rated about equally per unit of wound, and burn wounds should be rated far below these two.

Only one other point is needed to explain the differences in nutritional response found in this study—the differences in rate of wound healing. The skin excision wound represents maximal increment in obligatory heat loss with an extremely rapid rate of wound healing. The over-all result is only a moderate nutritional demand upon the animal. The burn-excision wound represents maximal increment in obligatory heat loss with a relatively slow rate of wound healing. The over-all result of this combination is a severe nutritional demand upon the animal. The burn wound represents a moderate increment in obligatory heat loss which starts slowly, reaching a peak with separation of the eschar. Combined with a relatively slow rate of wound healing, this results in a mild to moderate nutritional demand, not arising de novo but developing gradually.

By the same standards it becomes obvious that the slight increment in the rate of wound healing demonstrated by the B-E group over the B group did not compensate for the loss of the eschar. The increment in obligatory heat loss far exceeds the increment in rate of wound healing. The net result is a deleterious one for the animals.

These data constitute evidence that the relationship between a surface wound and its external environment is a dynamic one which significantly alters the energy balance of the animal which has sustained the injury.

CONCLUSIONS

1. The nutritional response of rats to sublethal wounds resulting in full-thickness skin loss is related to size of the wound produced, physical state of the wound (with or without eschar), and rate of wound healing.

2. Whichever combination of these 3 factors produces the least total obligatory vaporizational heat loss will eventually place the least total nutritional demand upon the injured animal.

3. The increment in the rate of healing of full-thickness burn wounds resulting from eschar excision on the fifth postinjury day is not due to an increase in the rate of wound contraction but to the earlier onset and/or more rapid rate of epithelization which occurs in the wounds from which the eschars are excised.

4. The intact eschars covering full-thickness burns in rats kept at an ambient temperature of 20° C. serve a definite function—heat conservation—which benefits the organism. This is accomplished by decreasing the extrarenal water loss occurring through the wound, and thus directly decreasing the obligatory vaporizational heat loss.

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Breast cancer and thyroid disease

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The observation of goiter in patients with cancer of the breast at the King County Tumor Clinic prompted further investigation of this subject. We have reviewed the epidemiologic data regarding the incidence of goiter and of breast cancer and we have reviewed certain experimental data which may have a bearing upon this problem. It is true that there are many errors and pitfalls in extrapolation from statistical data and from data gained in the experimental laboratory. Provided that one is aware of these limitations, it still may be possible to infer relationships which may prove useful as clues for future investigations.

METHODS

From December, 1957, until December, 1958, a careful physical examination of the neck was performed on nearly all the tumor patients seen at the King County Tumor Clinic. Records were kept of the admission rate and of the number of instances of breast carcinoma seen during that interval. Statistical material relative to the geographic variations in the incidence of breast cancer and of goiter was obtained for many places throughout the world and for the United States in particular. In addition to the statistical studies, other information was obtained from a review of the literature.

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RESULTS

Seventy-nine clinic patients who were afflicted with breast cancer were seen during this period. Table I shows the results of examination of them for thyroid disease.

Forty-two of the 79 patients appeared to have an abnormality of the thyroid gland which was evidenced by goiter in 37 and, in a few instances, by the fact that there had been thyroid operation or thyroid therapy in the past. No instance of hyperthyroidism was noticed. Most of the patients appeared euthyroid, while a few seemed hypothyroid or even myxedematous. The observation was made that the carcinoma in those who appeared euthyroid seemed to have a more benign course. Goiter was rare in the patients without breast cancer. It occurred in well under 10 per cent.

Statistical studies by others[17, 21] have called attention to global variations in breast cancer mortality rates. Countries with high rates are England and Wales, the Netherlands, and Switzerland (Table II). Low rates are found in Japan, Venezuela, Ceylon, and Chile. An apparent parallelism with goiter has been noted in the past.[20] A matching of the breast cancer rates with goiter rates suggests that goiter is prevalent in areas of high cancer incidence.[8] For example, western Europe, northwestern United States, central United States, and southwestern Asia have high rates of both breast cancer and of endemic goiter. Conversely, there is a low mortality rate where goiter is not endemic,[4] in Japan, Chile, southwestern United States, and Ceylon.

Table I. *Breast cancer patients examined for thyroid disease*

Findings	*No. of patients*
Breast carcinoma, palpable goiter	37
Breast carcinoma, history of thyroid therapy or operation but no goiter present	5
Breast carcinoma, no thyroid disease	33
Breast carcinoma, thyroid status unknown	4
Total	79

Table II. *Mortality rate statistics for breast cancer collected by Segi*[17]

Country	*Crude death rate*	*Age-adjusted death rate*
Denmark	31.6	20.2
England and Wales	36.3	19.1
Netherlands	25.3	18.6
Northern Ireland	26.6	18.4
New Zealand	27.7	18.2
Scotland	30.7	18.1
Canada	23.0	18.1
U. S. A., white	25.7	17.6
Union of South Africa (European)	20.8	17.4
Switzerland	29.4	17.3
Australia	23.8	16.1
U. S. A., nonwhite	16.0	14.8
Sweden	22.8	13.4
Israel	12.9	12.7
Norway	21.3	12.6
France	23.0	11.8
Germany	19.6	11.8
Austria	20.7	11.4
Italy	14.5	10.0
Finland	12.4	9.2
Venezuela	3.3	4.6
Japan	3.3	3.3
Ceylon	1.2	1.5

Statistical data on the geographical distribution of cancer mortality rates throughout the United States have been collected by the United States Public Health Service.[3] The distribution for all cancer, male, and all cancer, female, is indicated in Fig. 1. The over-all higher rates appear to come from the East, North Central, and Pacific Coast states. There are exceptions, however, and this is true with regard to cancer of the skin, pharynx, and buccal cavity. These types are more frequent in the South (Fig. 2). With respect to breast cancer there is apparently a distinct preponderance in the East, North Central, and Pacific Coast areas as compared with the rates in the southern states (Fig. 2).

Since these geographical variations in incidence have been noted, efforts have been made to find out whether or not there might be any detectable parameter. As mentioned before, we were drawn to consider endemic variation in goiter as a possible concomitant variant.[5] While admittedly little is proved and the whole subject is speculative at present, the data regarding goiter incidence have aroused our interest. Studies made from various sources published in the weekly Public Health Reports[14] indicate the prevalence of goiter in different portions of the United States. These data support the impression that there is a "goiter belt" existing throughout the East, North Central, and Northwest areas (Fig. 3).[15] Rates are considerably higher in the Northwest, for example, than in the South or Southwest. In particular, one might contrast the studies from the University of Washington with those from Cochise County, Arizona (Table III). The much higher rate in the university students is noteworthy. Cochise County is in southern Arizona, but the data appear to be consistent with those from the Navajo tribes in the northern part of Arizona, as reported by Salsbury.[16] The latter studies are of interest also because Salsbury has remarked on the great scarcity of breast cancer in the Navajo women. In general, moreover, one may infer that parallelisms exist between the mortality rates of goiter and of breast cancer. It is conceded that many spurious inferences may be drawn from the matching of statistical data. However, with the present treatment of cancer in an unsatisfactory state, the investigation of parameters related to incidence and causation continues to be warranted. The many hormonal implications of both breast cancer and of goiter lend further encouragement to this form of study.

Lacassagne[9] stated that the ovary and pituitary gland are requisite to the development of breast cancer and this is probably

basically true. The thyroid gland has received less attention. However, it appears that experimental thyroid deficiency results in hyperestrinism. Thus, if it is accepted that hyperestrinism is important to breast cancer and that experimental thyroid deficiency may cause hyperestrinism, then a basis for further study of this aspect of thyroid physiology may exist.[18] Historically, it is interesting that Beatson[1] found goiter in his patients and used thyroid extract as an adjunct to therapy by castration.

Experimental work relating the thyroid gland to the ovary and breast has been carried out. Leonard[10] showed that "the follicle stimulating hormone prepared from the hypophysis and urine and free from the thyrotropic hormone is more effective in the absence of the thyroid. The ovaries are from 38.1 per cent to 160.6 per cent heavier and contain only follicles. The larger ovaries in the thyroidectomized rats produce greater amounts of female sex hormones as the uteri of the thyroidectomized animals are from 55.8 per cent to 185.3 per cent heavier than those of the controls." Smithcors[19] concluded from his experiments that "the general effects of thyroidectomy on mammary growth in immature rats are (a) an inhibition of duct extension, (b) the production of a small compact type of gland with thickened ducts, and (c) a marked development of the lobular-alveolar system." Morris,[12] however, in his experiments found that "the appearance of the tumors (mammary) was delayed in the thiourea treated group." Miller's[11] study disclosed that "in the thiourea-fed group hepatomas occurred in five of ten mice without ovarian tumors, but in only one of ten ovarian tumor-bearing mice. The presence of ovarian tumor in this group was associated in every mouse with the presence of large amounts of an estrogen hormone in the peripheral circulation and even large amounts going directly to the liver." Muhlbock's[13] experiments have shown that continuous treatment with estrogen is much more effective in the induction of mammary tumors than discontinuous treatment. Thus, it can be seen that certain experiments suggest increased ovarian activity in the presence of disturbed thyroid (hypothyroid) function. The importance of continuous administration may lend increased significance to the biologic production of increased ovarian activity.

Studies by Furth[6] reveal that I^{131} destruction of the thyroid gland has pronounced

Table III. *Distribution of endemic goiter in the United States as shown by thyroid surveys*

		No. examined			*Percentage with goiter*				
Place	*Ages*	*Boys*	*Girls*	*Boys and girls*	*Boys*	*Girls*	*Boys and girls*	*Reported by*	*Remarks*
Arizona									
Cochise County	15-18			3,500			0.08	R. B. Durfee	Not a local problem
Washington									
Montesano	11-18			159			27.04	D. C. Hall	
	5-14			466			23.42		
Seattle	5-14				42.0	48.0			
	14-18	575	521		38.3	65.6			
Tacoma	8-20			310			10.6	W. J. Kerr	Indians
Chelan County	5-14			2,000			46.5	P. T. West	
Yakima County							46.0	H. H. Smith	Circular letters
State	12-18				65.0	75.0		J. T. Mason	Estimate
Camp Lewis		21,182			21.0			W. J. Kerr	
University of Washington				13,000	26.37	33.2		D. C. Hall	1914

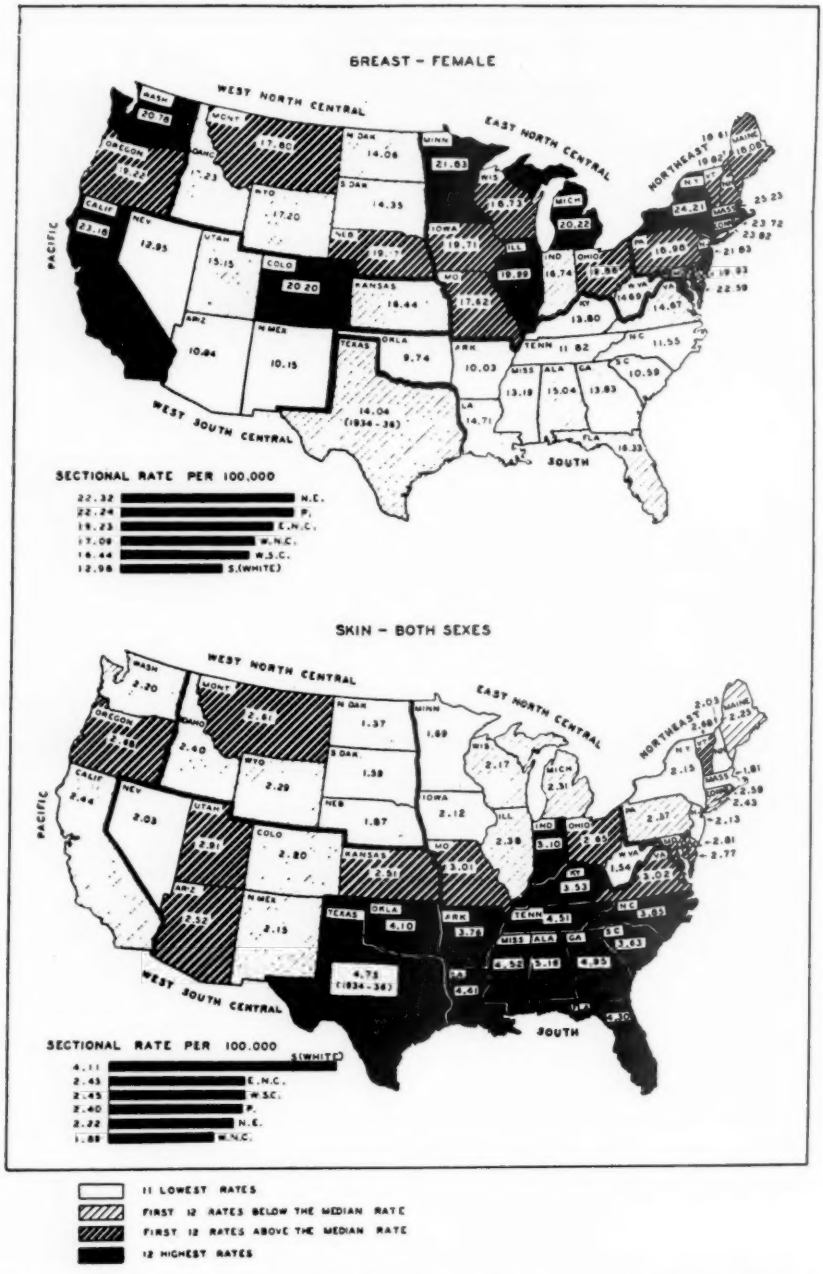

Fig. 1. Death rates per 100,000 all cancer, male and female, in the United States.

gonadal, uterine, and mammary effects. His comments are worth quoting in detail:

> The minor gonadotrophic side effects of thyrotropes can cause a profound change if the level of this hormone is steadily maintained at formidable heights (thousands if not tens of thousands of times normal). This is the situation in athyroid animals bearing large dependent tumors in which the weight of the ovaries increased ten-fold to one hundred-fold, the uterine horn is markedly enlarged, the mammary gland is stimulated, and the pituitary is swollen with poorly granulated eosinophils. In hypophysectomized hosts, the extraordinary ovarian hyperplasia is present, but stimulation of the mammary gland is not. This clearly illustrates Claude Bernard's principle of determinism in which a change causes a secondary event, and that a tertiary event, and so on until death ensues. In the present case, I^{131} destroyed the thyroid, causing lack of thyroid hormones.

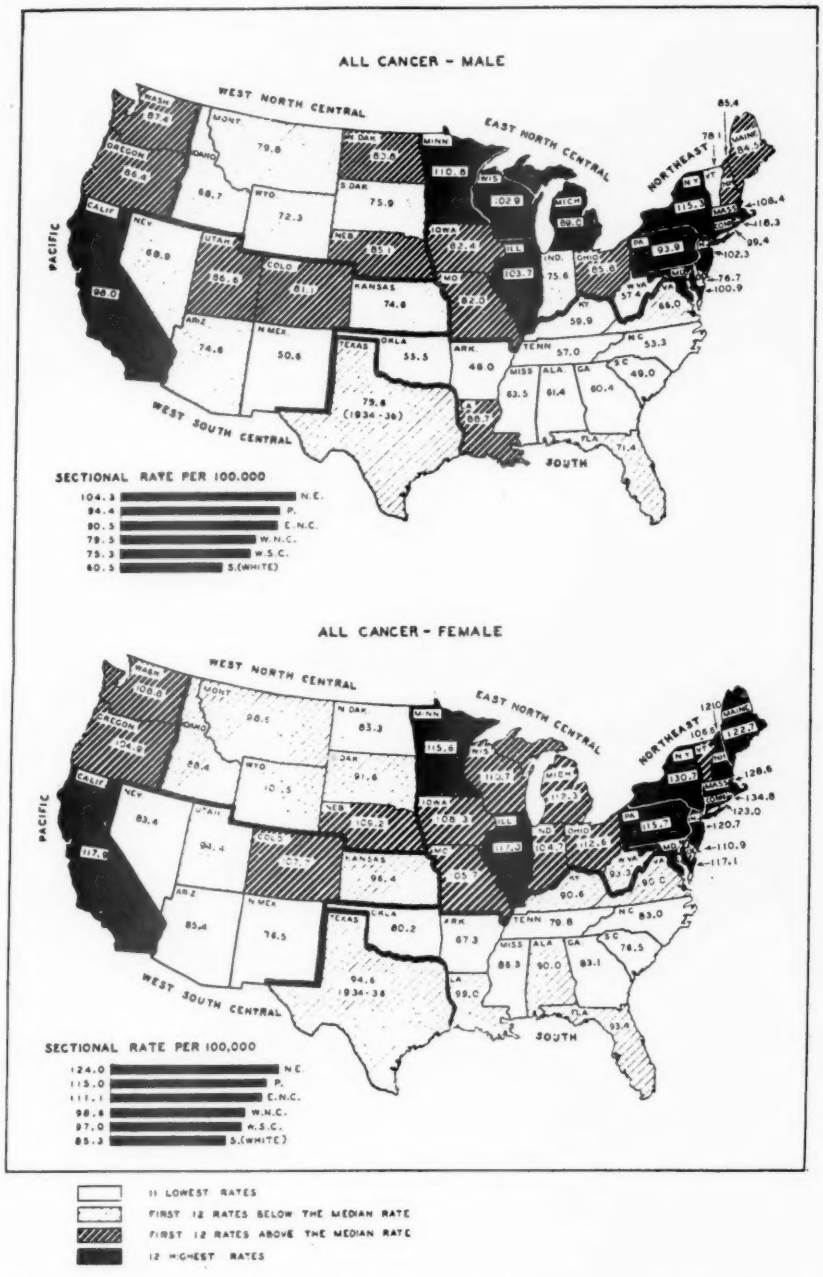

Fig. 2. Distribution of death rate in the United States for skin (both sexes) and breast (female) cancer.

This led to hyperplasia of thyrotropes followed by dependent-tumor formation with excessive discharge of estrogens that in turn stimulated the mammotropes, and ultimately caused hyperplasia of the mammary gland (perhaps in breasts that had been "prepared" by estrogens). Thus can a single event, intake of I^{131}, initiate a pluriglandular disturbance. Evidence is accumulating in support of the theory that the primary force in the induction of mammary tumors is the mammotrope and that estrogens are the specific stimulants of the mammotrope, exerting their effects mainly by indirect action.

Should prolactin be involved in this problem, certain interesting phenomena which have been noted by others may be relevant. Iodination of prolactin appears to suppress to some extent lactogenic activity.[22] Whether

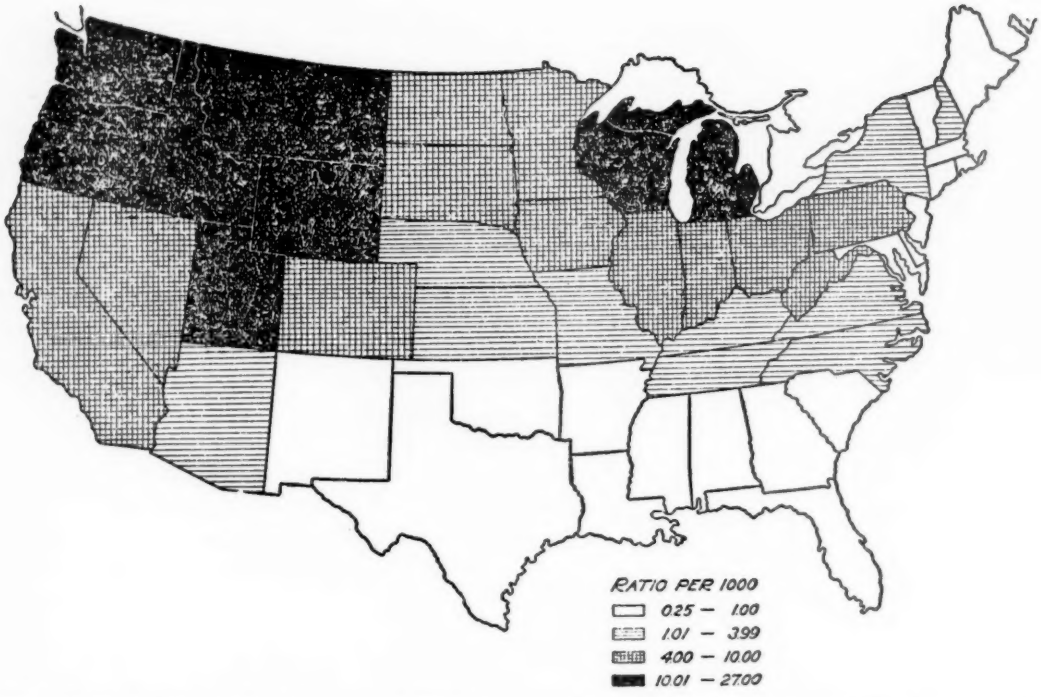

Fig. 3. Ratio of simple goiter per 1,000 men examined for military service, based on a total of 2,510,701 examinations.

variations in iodine supply are clinically important in this regard is not known. Also, prolactin has an interesting phylogenetic background in that it is found relatively "early" in phyla and long before the appropriate target organ has made its appearance[7] (Table IV). The phylogenetic variations in hormones suggests that there may be implications here of significance in medicine.

DISCUSSION

The progressive development of organismal complexity can be seen in certain biochemical histories. For example, iodine is present in elementary form in diatoms. In the coral sponges iodine is present in 3,5-diiodotyrosine, while in the lamprey, iodine is incorporated in thyroxine. As hormonal mechanisms appear on the biologic stage, it becomes apparent that more complex endocrine controls are set up. By the same token, more of the individual cell autonomy and regulating devices are sacrificed to highly specialized mechanisms. Thyroxine is a striking case in point.

While large areas of uncertainty exist, it well may be that the incidence of neoplasia, and especially malignant neoplasia, tends to reflect the introduction of increasingly complex endocrine controls. From this point of view, the single cell and other so-called primitive forms of life are in reality more "whole" and "complete" forms, with perhaps simpler but more stable intrinsic cell mechanisms. When increased specialization and extreme complexity are introduced, disruptions of normal processes may be more likely to occur, with disordered function and anarchic reproduction. While this concept is speculative and may have only limited application in cancer even if true, it is suggested that a fruitful field for investigation would be the phylogeny of the group of tumors which are known to be hormone dependent.

We are inclined to believe that the complex of endocrine controls may be of importance in setting the stage for the development of certain of the hormone-dependent tumors. We also believe that the view of Bern[2] may be pertinent in this regard. He stated that "the following general possibilities emerge from recent studies of mouse mammary cancer: (1) hormonal factors in-

volved in the evolution of a definitive precancerous state may be no more than those factors involved in normal tissue development; (2) the tumorigenic role of the hormonal milieu may be no more than the continued maintenance of a degree of hyperplasia (the precancerous state); (3) the so-called tumorigenic hormone may be but one component of an essential milieu wherein no one hormone can be considered more essential than any other; (4) in general, the hormonal influence may be a 'permissive' one, essential for tumor appearance but not itself inductive."

SUMMARY

Clinical and epidemiologic studies raise the question of whether there might be a positive correlation between the incidence of goiter and the incidence of breast cancer. It appears that areas plagued with goiter tend to have a high breast cancer mortality rate. Conversely, areas with a low incidence of goiter seem to have a low breast cancer fatality rate. While such evidence is far from conclusive, it may be justifiable to regard the data as provocative and meriting further inquiry.

From the experimental laboratory there is evidence that impairment of thyroid function may affect the mammary gland to a considerable degree. This effect upon the breast appears to be mediated through the ovary secondary to pituitary activity which has been initiated by the thyroid dysfunction.

Table IV. *The known occurrence of pituitary hormones*

	Chromatophorotropin	*Gonadotropin*	*Thyrotropin*	*Adrenotropin*	*Growth*	*Prolactin*	*Diabetogenic*
Crustacean eye-stalk	+ (2)	—	—	—	—	—	—
Insect corpus allatum	—	+ (92) (73)	—	—	—	—	—
Ascidian subneural gland	—	+ (44) - (13)	—	—	—	—	—
Cyclostome	+ (99)	—	—	—	—	—	—
Elasmobranch	+ (58) (1)	—	—	—	—	—	—
Teleost	+ (1)	+ (46) (21) (49) (9) LH (97)	+ (37)	—	—	+? (52)	—
Amphibian	+ (Many reports) (1)	+ (Many reports) (48) (98) (27)	+ (85) (5) (4)	+ (20) (74)	+? (34)	+? (52) (35)	+ (47) (84)
Reptile	+ (50) (1)	+ (46) (78)	+ (78) (43)	—	—	+? (52)	—
Bird	+ (32) (51)	+ (Many reports) FSH (54) (65) LH (96) (54)	+ (96) (86) (37)	+ (65)	—	+ (52) (80) - (65)	—
Mammal	+ (Many reports)	+ (Many reports) FSH (Many reports) LH (Many reports)	+ (Many reports)	+ (Many reports)	+ (Many reports)	+ (Many reports)	+ (Many reports)

The possibility exists that goiter may indicate an endocrine abnormality of significance in human breast cancer. It appears to us that continued intensive study of the hormonal aspects of breast cancer is in order and also that a study of the phylogenetic relationship of hormone development to neoplasia might be warranted.

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The value of surgical removal of localized lymphomas

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The thesis that malignant lymphomas may be successfully treated and ultimately cured by the use of total surgical extirpation is not generally accepted. There is a strong belief that this type of malignant disease is a generalized, systemic disease even from its earliest beginnings. In 1926, Des Jardins[9] stated that cure of lymphomas was impossible because of their systemic nature. Minot[24] and others propounded that surgical treatment or any other type of therapy was of no avail and resulted in nothing more than varying degrees of palliation with no effect on eventual prognosis or survival time. As late as 1936, Krumbhaar[19] stated that these conditions "are practically all alike in having a fatal prognosis although the duration may extend from a few days to many years."

Conversely, others believe that many patients, if aggressively treated while the disease is in a clinically localized stage, could secure a permanent cure. In 1917, Yates and Bunting[32] were the first to champion the surgical removal of all disease as treatment when disease was apparently localized. Jackson and Parker,[17] in 1947, stated in their classic book on the lymphomas that there were no valid grounds for assuming that this type of neoplasia represents a systemic disease at its onset. They believe that the tumor often begins in one focus and then disseminates to other locations at extremely variable rates. They explained the poor prognostic outlook and the eventual occurrence of generalized involvement by stating, "Too often, however, one hesitates, argues and procrastinates until the time comes when it can be truthfully said that operative interference is uncalled for. Too often one waits to see what will happen. Such is the early history of many an incurable disease. The paradox is that when the lymphadenopathy is still possibly amenable to complete surgical removal, it is liable to be regarded as benign, whereas when it has become inoperable one contents oneself by saying that it has always been so."

Perhaps the greatest contribution to the thesis that lymphomas often begin as unicentric localized disease and may remain so was supplied by Gall and Mallory[13] from their necropsy studies of patients who had died from these conditions. In the 135 cases studied, localized disease could have been removed surgically in approximately 10 per cent. In the opinion of Gall and Mallory, malignant lymphomas should not be regarded as systemic diseases at the onset, but as unicentric in origin, spreading to other foci at extremely variable rates. Lumb,[20] in a study of 602 cases, showed that the 5-year survival rate of patients with localized disease was remarkably good, approximately 52 per cent. He states that in Hodgkin's disease, dissemination often followed an orderly pattern from one lymph node group to the most proximal node group.

Pursuing his findings in necropsy studies, Gall[12] published a report on the value of the surgical treatment of lymphomas. He reported that in a series of 48 patients in whom all gross evidence of tumor had been removed, the median survival time was 5.2 years, which was twice that of a comparable group who had received only x-ray therapy. The 5-year survival rate in the surgically treated patients was 41 per cent and the

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average total duration exceeded all expectations—9 years from the onset of disease. Sugarbaker and Craver[28] in 1940, Slaughter and Craver[26] in 1942, and Hellwig[15] in 1947, published papers with findings supporting the surgical removal of all gross tumor when clinically localized. Sugarbaker and Craver reported a 5-year period of survival in 24 per cent of patients with localized malignant lymphoma who had undergone early surgical treatment. Hellwig, using radical surgical treatment alone, secured a 67 per cent 5-year survival rate in 21 patients with a single primary focus of disease. Craver[7] agreed that often patients will present themselves while the disease is in a localized stage and that aggressive therapy in these cases is definitely indicated. He stated, however, that there was no convincing evidence to confirm the superiority of surgical extirpation over x-ray therapy. He did not object to the surgical removal of a single large localized mass, as this would eliminate the need for obliterative doses of irradiation. However, he advocated restriction of surgical treatment to Hodgkin's disease localized to the upper cervical region, and believed it should always be followed with postoperative irradiation. Most proponents of surgical therapy believed that it should be limited to patients (1) who have involvement of only one lymph node group, organ, or area, (2) whose tumor is resectable, and (3) who have no systemic signs or symptoms.

Accepting its possible curative value, Slaughter[26] noted that if the results of surgical therapy could even equal the results of irradiation, it should be used because the effects of an operation are permanent, whereas the side effects of irradiation not only are permanent but also may be progressive. Marshall[21] and others[11] believed that it is especially dangerous to use irradiation on patients with massive involvement of the viscera, because severe and often fatal hemorrhage is a frequent complication.

Good results with surgical therapy have been reported in the treatment of localized disease affecting the gastrointestinal tract. Crile[8] has compiled a 68 per cent 5-year survival rate in patients with lymphosarcoma of the stomach treated by subtotal resection and postoperative irradiation. Marshall[23] reported a 5-year survival rate of 33 per cent in patients who had undergone total gastric resection for localized malignant lymphomas and a rate of 42 per cent in those who had had partial gastric resection. Warren,[30] using subtotal gastrectomy and postoperative x-ray therapy, also secured a 40 per cent 5-year survival rate in patients with gastric lymphomas. Allen and associates[1] achieved a 43 per cent 5-year survival rate in 79 patients with gastrointestinal disease who had undergone radical gastric resection followed by irradiation. Of patients with lesions localized to the stomach there was a 58 per cent survival rate although almost half had perigastric nodal involvement and half had residual tumor at the margin of resection. These authors were of the opinion that their findings do not preclude cure provided that intensive postoperative irradiation is used. Fraser,[11] investigating lymphosarcoma of the stomach, reported a 39 per cent 5-year survival rate in patients with gastric resections followed by irradiation while of comparable patients treated with x-ray alone, all were dead within 12 months.

Most authorities have found that Hodgkin's disease of the gastrointestinal tract carries a much more serious prognosis than lymphosarcoma or reticulum cell sarcoma. Marshall[23] reported a 53 per cent survival rate in lymphosarcoma while in Hodgkin's disease, the rate was 27 per cent for 5 years. It is also to be noted that lesions of the small intestine, colon, and rectum have a decidedly worse prognosis than those of the stomach. Falkner and Dockerty[10] reviewed the cases of lymphosarcoma of the small intestine recorded at the Mayo Clinic and found only a 21 per cent 5-year survival rate after resection and postoperative irradiation.

The degree of localization of gastrointestinal lymphomas is difficult to assess. In many cases regional node enlargement is noted but only 40 to 50 per cent of the enlarged nodes contain tumor. Also, Warren[31] found that although many patients with

marked submucosal spread did not have clear margins of resection, postoperative irradiation yielded results which did not appreciably differ from those in patients who were free of node involvement and had clear margins. Warren[31] noted that approximately 20 per cent of the lesions are multicentric in origin and that a thorough search for other intestinal lesions should be made at celiotomy.

Localized lymphomas involving soft tissue and lymph node groups of the head and neck, axillae, inguinal regions, and other parts of the body have also been treated by radical surgical means with and without postoperative irradiation. In 1940, Baker and Mann[2] reported 2 cases of cervical Hodgkin's disease in which the patients had been free of active disease for periods of 10 and 12 years after radical surgical removal and postoperative irradiation. In 1942, Slaughter,[26] discussing surgical treatment of Hodgkin's disease, cited 4 cases of lesions localized to the cervical region which were successfully managed by radical surgical removal alone. In a follow-up of this study[27] in 1958, he reported 11 5-year surivals ranging from 6 to 13 years postoperatively in 18 patients who had undergone radical operations, a survival rate of 60 per cent. Seven of the 11 survivors had had surgical treatment alone without subsequent irradiation.

Primary lymphoma of the thyroid gland is relatively unusual. There are only 108 cases reported in the literature. Walt[29] reported 21 cases which had been managed by radical resection and postoperative x-ray treatment with a 37 per cent 4-year survival rate.

Lymphomas involving the lung and mediastinum have also been treated, when technically feasible, by resection of the involved lobe or lobes and mediastinal dissection with and without postoperative irradiation. In 1946, Blades[4] described 109 cases of mediastinal tumors, 4 of which were Hodgkin's disease and 2 of which were lymphosarcoma involving only the mediastinum. In 3 of these cases the lesion could be resected and when last observed the patients were free of disease. More recently,[14] he has reported 3 cases of primary lymphosarcoma of the lung. One patient treated by pneumonectomy is alive and well 8 years after the operation. In the other 2 the lesions were not suitable for surgical extirpation. Beck[3] reported survival ranging up to 30 months postoperatively in 89 per cent of 11 patients with pulmonary lymphomas treated by surgical extirpation, with all patients being free of disease. He states that these lymphomas are usually slow growing, do not metastasize until very late, and tend to spread locally to involve mediastinal structures. Rose[25] reviewed a series of 17 cases of lymphosarcoma of the lung in which the patients were treated surgically. He found a 45 per cent 5-year survival rate and only 1 patient actually died of his disease. All patients who could not be operated upon but were treated by irradiation were dead within 12 months. Rose emphasizes the similarity between the clinical course of these lesions and that of lymphosarcoma of the stomach, which often remains localized for long periods and may be cured by operation. Cooley,[6] in reviewing the Mayo Clinic series of cases of primary lymphoma of the lung, reported that 50 per cent of patients successfully operated upon were alive and without evidence of disease after 5 years. Of the patients who had been treated by irradiation only, there was 1 alive and free of disease.

Primary lymphoma of the bone seems to be restricted to the reticulum-cell sarcoma type and is relatively uncommon. Coley[5] reported a 47 per cent 5-year survival rate in 21 patients treated by irradiation. Jackson and Parker,[18] having secured an 83 per cent survival rate for 8 to 13 years, advocated amputation and roentgen-ray therapy. In a comparable study, they employed amputation alone, compiling a 60 per cent 5-year survival rate with absence of disease. Ivins[16] employed amputation or radical excision followed by x-ray therapy and obtained a 35 per cent survival rate for 5 years. Despite Jackson and Parker's findings, however, much of the literature implies that ampu-

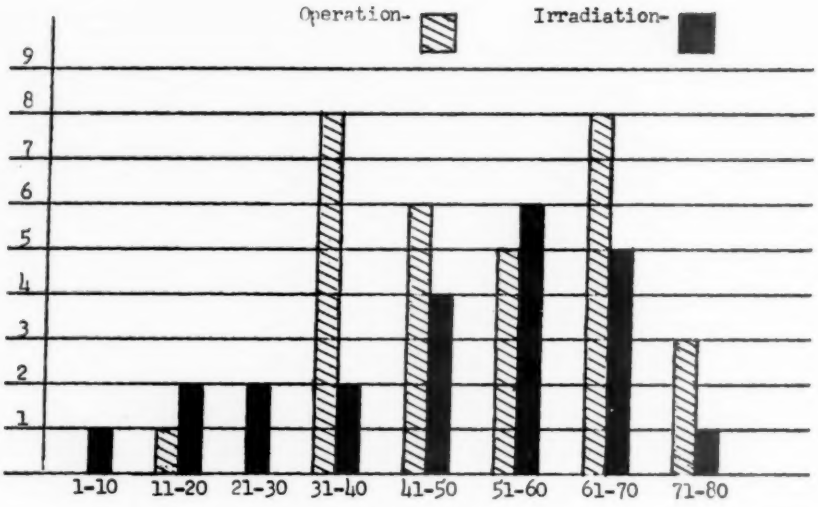

Fig. 1. Age distribution.

tation is usually not justifiable and that radical excision with postoperative irradiation is the therapy of choice.

The present study began as a review of all cases of malignant lymphoma seen at The George Washington University Hospital during the period from 1947 to 1960 but the case histories of only patients with clinically localized lymphoma are included in the statistics. Patients treated by surgical removal of all disease, with and without postoperative roentgen-ray therapy, were compared to those treated by roentgen-ray therapy only. In our series, the patients listed as having had surgical treatment are those in whom complete removal of the lesion, either by simple excision or by more radical procedures, was performed. Patients who had only biopsy or partial resection of tumor and subsequent irradiation therapy are not considered to have had surgical therapy. The patients treated by roentgen-ray therapy alone received tumor doses ranging from 1,760 r to 14,400 r with an average of 3,535 r and a median dose of 3,000 r. Therapy was given by various radiologists throughout the metropolitan area as well as in several medical centers throughout the country. The details of treatment factors were not available for inclusion in this report.

A total of 214 lesions were diagnosed as lymphoma but of these only 54, or 25 per cent, were clinically localized at the time treatment was begun. Only the latter are included in the study. The patients had disease clinically localized to either one lymph node, one lymph node group, a single viscus, or a single area of localized soft tissue or bone. Each patient had a normal chest roentgenogram, normal results of blood and urine studies, and no systemic signs or symptoms.

Results of treatment are given in Table I. The treated groups are comparable with regard to operability as well as histologic types. Twenty-two of 31 patients treated by surgical removal of disease are living and well as compared to 2 of 23 patients who received only roentgen-ray therapy.

Fig. 1 indicates that the age distribution for the 2 primary groups, operation and irradiation, is comparable. The average age for the operation group is 51 years as compared to 47 years for the irradiated group, while the median age is 48 and 51 years, respectively.

Table II shows the average survival times in the 3 classifications. The group treated by operation received therapy relatively recently, as 12 of 13 patients have been alive for an average of 45 months since treatment was begun. Of the surgically treated patients who received postoperative

irradiation, 10 of 18 are alive. Only 5 of the 23 patients treated with irradiation alone are living and have prospect to increase the survival rate of their group.

As indicated in Tables III and IV, more patients are now alive and have survived 5 years without evidence of disease in the surgically treated group than in the group treated by irradiation. No patient of either group died of causes other than the lymphoma.

The locations of disease in patients treated by roentgen-ray therapy only and patients treated by operation were also comparable. It is to be noted that there was a 90 per cent 5-year survival rate in patients with lymphomas of the peripheral lymph nodes treated by total excision as contrasted to a rate of 19 per cent in those treated by roentgen-ray therapy. This was the group in which surgical therapy was most successful. Some patients with visceral lesions also were treated successfully by surgical removal but not as frequently as when the disease was localized to peripheral lymph node groups.

There are now 12 survivors who have been free of disease for more than 5 years. Ten had surgical therapy and 2 had irradiation alone. The 5-year cure rate for patients free of disease is 56 per cent for the surgical group as contrasted to 9 per cent for the irradiated group. Of the 28 treatment failures, 8 were with operation and 20 were with irradiation.

As shown in Table VI, 5-year survivors are represented in each of the different histologic groupings. Ten of the 14 in the surgical group and 2 of the 7 in the roentgen-ray therapy group are, in addition, free of disease.

Radical surgical therapy does not appear to be a better form of therapy than nonradical. Six of 10 patients who underwent radical operations (such as radical neck dissection) are presently alive and well while 16 of 21 who had only complete total excision of all discernible disease are alive and free of disease. Ten of the 21 who had excision had postoperative roentgen-ray therapy and 8 of the 10 who underwent radical procedures had additional roentgen-ray therapy. However, 5 of the 16 surviving patients treated by nonradical procedures had giant follicular lymphomas, which are generally thought to be a more benign type of lymphoma with a better prognosis. No patients with giant follicular lymphomas received radical therapy.

Table VII is a summary of the various statistics for comparison. These figures indicate that patients who had surgical removal of their disease fared much better than those who had irradiation with operation or irradiation alone.

Table I. *Type of treatment utilized and present status of patients*

Lesion	*Living and well/total*		
	Operation	*Operation + irradiation*	*Irradiation*
Hodgkin's disease	3/3 (100%)	3/5 (60%)	0/6 (0%)
Lymphosarcoma	2/2 (100%)	3/5 (60%)	1/7 (14%)
Reticulum-cell sarcoma	4/5 (80%)	2/6 (33%)	1/8 (12%)
Giant follicular lymphoma	3/3 (100%)	2/2 (100%)	0/2 (0%)
Totals	12/13 (92%)	10/18 (56%)	2/23 (9%)

Table II. *Average survival time in months after initial therapy*

Lesion	*Operation*	*Operation + irradiation*	*Irradiation*
Hodgkin's disease	24	94	49
Lymphosarcoma	66	72	43
Reticulum-cell sarcoma	34	72	35
Giant follicular lymphoma	64	75	49
Averages	45	74	42

Table III. *Patients with localized lymphoma alive and free of disease at present after operation and irradiation*

Lesion	Operation		Irradiation	
	Total No.	%	Total No.	%
Hodgkin's disease	6	75	0	—
Lymphosarcoma	5	70	1	14
Reticulum-cell sarcoma	7	55	1	12
Giant follicular lymphoma	6	100	0	—
Totals	22	71	2	9

Table IV. *Five-year survival rates of patients with localized lymphoma treated by operation or irradiation**

Lesion	Operation (%)	Irradiation (%)
Hodgkin's disease	75	60
Lymphosarcoma	100	29
Reticulum-cell sarcoma	57	12
Giant follicular lymphoma	100	50
Over-all	77	32

*Not all patients are free of disease.

Table V. *Relationship of location of localized lymphoma to survival and type of treatment**

Location	Operation	Operation + irradiation	Irradiation
Peripheral lymph nodes	9/9	6/9	0/17
Viscera	1/1	2/6	1/4
Soft tissue or bone	2/3	2/3	1/2
Totals	12/13	10/18	2/23

*Expressed as living and well/total.

Table VI. *Histologic type of localized lymphoma in patients treated by operation or irradiation and surviving more than 5 years*

Lesion	Operation	Irradiation
Hodgkin's disease	3	3
Lymphosarcoma	5	2
Reticulum-cell sarcoma	4	1
Giant follicular lymphoma	2	1
Totals	14	7

DISCUSSION

It appears that in this series the groups described are comparable in all important respects and therefore are suitable for comparative analysis. The findings strongly suggest that the surgical removal of all grossly discernible tumor has a most beneficial effect on the eventual course and prognosis of patients with localized lymphomas. The study further suggests that while a few patients who receive only irradiation for localized and resectable disease may survive for an appreciable length of time, most of these patients do not remain free of disease for any long period of time. In our series it is predominantly in cases in which complete surgical extirpation of disease was carried out that complete and possibly permanent freedom from disease was achieved.

The place of postoperative irradiation cannot be evaluated from this study. The figures compiled suggest that it is of questionable merit in that patients who received postoperative irradiation fared no better than those who did not. In point of fact, those who did not receive irradiation actually did better statistically than comparable patients who received it. However, the series is small and at least one important variable has not been controlled, namely, the variable of time. The surgical patients *without* irradiation were treated an average of only 45 months ago as compared to 74 months in the surgical patients who received roentgen-ray therapy. It may well be that in another period of 2½ years, the comparison will be different indeed.

Our findings certainly imply that irradiation alone, *in the manner administered,* was not nearly as effective as surgical procedures in the management of localized lymphoma. There are 3 possible explanations—first, that the removal of all tumor per se is the important factor in achieving cure, second, that roentgen-ray therapy as given in this study really has no worth-while effect, or, third, that roentgen-ray therapy *in the manner administered* may actually have been deleterious.

Table VII. *Summary of the characteristics of localized lymphomas studied and the results of methods of treatment*

	Operation	*Operation + irradiation*	*Irradiation*
No. localized	13	18	23
Average size of lesion	4.8 cm.	4.0 cm.	3.9 cm.
Average age of patients	40 yr.	58 yr.	47 yr.
Median age of patients	42 yr.	59 yr.	51 yr.
Average survival time	45 mo.	74 mo.	42 mo.
No. of patients alive*	12	10	2
Per cent alive*	92%	56%	9%
5-yr. survival rate	75%	79%	32%
5-yr. survival*	3	7	2
Per cent 5-yr. survival*	75%	50%	9%

*No evidence of disease.

Of these possibilities our results suggest that the complete, but not necessarily radical, removal of all disease is the important factor in achieving cure. There is certainly no reason to assume that all forms of roentgen-ray therapy are harmful in the treatment of these conditions, for many authors have reported respectable survival rates. However, a question is raised by this study, namely, can some forms of roentgen-ray therapy be harmful and accelerate the course of these diseases, and could our findings be explained on this basis? A somewhat superficial investigation of the irradiation data secured so far indicates that in general the tumor doses delivered and the kilovoltages employed were somewhat less than are used by others in the field who have reported greater success. This aspect of the study is being further pursued and will be reported subsequently. The understandable lack of untreated control patients and the relatively small total number of cases make opinions of this sort extremely difficult to substantiate. Nonetheless, the excellent results which have been secured through complete surgical removal of localized lymphoma as shown by this study definitely indicate that the prognosis in these cases can be good, at least in certain instances. While the total number of cases is too small to permit a significant statistical evaluation, these results, which cover 12 years of experience in a large university hospital, demonstrate the need for similar studies in other institutions so that a sufficiently large series can be accumulated to allow accurate statistical evaluation. The present studies, however, do demonstrate that, contrary to some opinions, many patients with localized lymphoma can be and have been successfully treated by complete surgical removal. Therefore, localized lymphoma can and probably should be managed in the same manner as early carcinoma, that is, by total surgical extirpation.

SUMMARY

1. The results of a study comparing the effectiveness of treatment of localized lymphomas by irradiation with treatment by surgical removal, with and without postoperative irradiation, is presented.

2. The statistics derived indicate that patients who receive the benefits of surgical removal of all known disease have a much better prognosis than those who receive roentgen-ray therapy alone as given in the cases in this analysis.

3. The evidence suggests that in many instances the lymphomas will begin and remain in a localized stage which is amenable to aggressive surgical therapy and that this therapy can prevent further progression and dissemination of the disease process.

4. The study suggests that nonradical operations, provided that there is complete removal of all lymphomatous disease, may achieve cure as readily as more radical procedures.

5. Further investigation of the possible effects of irradiation when given by difficult

techniques and dosages may be of extreme importance and will be pursued further in subsequent studies.

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Splenic trauma: an increasing problem

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Throughout the ages the spleen has been associated with violence and trauma. According to Carstens,[4] in 1590 Dr. Viard removed a spleen through a side wound with recovery of the patient. In 1600 a barber removed a portion of a spleen which protruded through a wound and the patient recovered. Hannaeus, in 1698, removed a spleen protruding through a knife wound and his patient also recovered. In 1737 Ferguson partially removed a spleen that was ruptured. Bailey[1] reports that Riegues of Breslau performed the first successful splenectomy for rupture in 1893. According to Bueermann,[2] the first splenectomy performed in the United States was by Brown in 1814, and the first for ruptured spleen was by Riegner in 1893. One method of assassination in China, where diseased spleens were common, was to strike a man over the splenic area. Since the diseased spleens were easily ruptured, the injured man usually died of hemorrhage within hours. During the past 50 years, with the environment increasingly conducive to both military and civilian trauma, splenic injury has continued to present a serious problem in surgical management.

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THE INCREASING INCIDENCE OF SPLENIC TRAUMA

Over the past 10 years 90 splenectomies have been performed at the United States Naval Hospital, Portsmouth, Virginia. The leading indication was splenic trauma in 60 per cent, followed by primary medical disease in 31 per cent (Table I). Splenic trauma has increased markedly in incidence during the 10-year period (Fig. 1). The low ratio of 1 in 21,700 admissions in 1951 differs markedly from the high of 1 in 1,762 in 1959. The ratio of splenic trauma to general surgical admissions has increased over the past 5 years (Fig. 2). The low recorded was in 1956 with 1 in 1,139, and the high in 1959 with 1 in 193.

TYPES OF SPLENIC TRAUMA

Of 54 cases (Table II), immediate rupture ocurred in 38 with 6 deaths. Delayed traumatic rupture, described by McIndoe[8] as rupture followed by complete or almost complete cessation of hemorrhage (a minimum

Table I. *Indications for splenectomy, United States Naval Hospital (1949 to 1959)*

	No. of cases	*%*
Splenic trauma	54	60
Primary medical diseases	28	31
Secondary to other surgical procedures	8	9
Totals	90	100

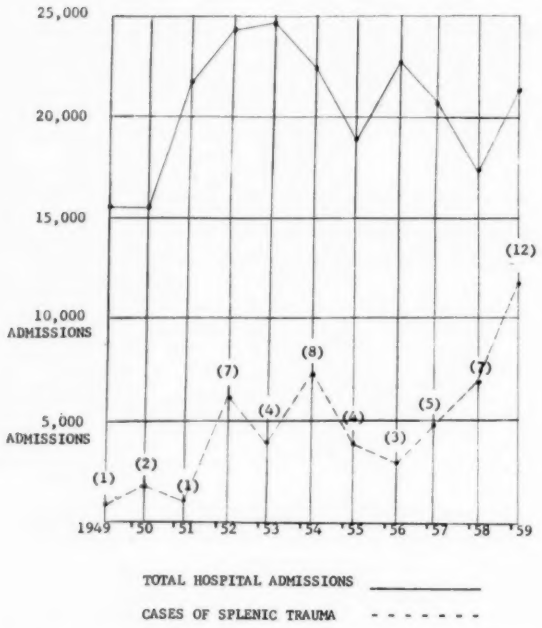

Fig. 1. Incidence of splenic trauma in total hospital admissions.

of 48 hours) followed by renewed profuse secondary hemorrhage, was seen in 12 cases with 1 death.

Comparison of immediate and delayed rupture. The diagnostic accuracy (Table III) leaves something to be desired. The largest number of patients with immediate rupture were admitted as "diagnosis undetermined" (ruptured spleen), with the correct diagnosis being apparent in 8 per cent. There is a frequent association of injuries to the genitourinary tract, recorded as "diagnosis undetermined" (ruptured kidney, ruptured bladder, or hematuria). In cases of delayed rupture the most common diagnosis was "intracranial injury" (35 per cent). The correct diagnosis was made in 17 per cent.

The types of injuries (Table IV) can readily be applied to civilian as well as military patients. The majority resulted from auto accidents. In cases of delayed rupture, auto accidents accounted for 44 per cent. One case resulted from striking the left flank on a kitchen cabinet. In another, the only detectable trauma was severe coughing which had been associated with a cold for approximately 1 week prior to the onset of sudden and severe intra-abdominal discomfort.

Of the leading complaints and physical findings (Table V), it is significant that 100 per cent of the patients able to recite in both the immediate and delayed rupture groups had persistent and usually progressive abdominal pain and discomfort. On physical examination 74 per cent demonstrated generalized abdominal rigidity and tenderness, whereas 66 per cent demonstrated rebound tenderness with referral to the left upper quadrant of the abdomen. In patients with delayed rupture, 41 per cent complained of left shoulder pain, 25 per cent of left lower chest pain and dyspnea as well as nausea and vomiting. Fifty per cent had sudden discomfort of a very severe nature. Thirty-three per cent had fainting and weak spells, the majority for several days prior to admission.

Other diagnostic aids (Table VI) yielded few significant findings. Laboratory studies were of more value than roentgenograms.

Abdominal paracentesis has been found to be of little value as a diagnostic aid. False-negative taps encouraged unwarranted delay with tragic results in 1 case. We agree with Harkins[6] that in cases of doubt an exploratory incision is preferable to blind paracentesis.

ASSOCIATED INJURIES

In 29 per cent of the patients with immediate rupture, fractured ribs (left, commonly multiple), were present (Table VII). Extremity fractures and laceration of the

Table II. *Types of splenic trauma (54 cases)*

Type	*No.*	*% total*	*Deaths*	*Mortality rate for each type (%)*
Rupture, immediate	38	70	6	16
Rupture, delayed	12	22	1	8
Traumatic cyst	2	4	0	0
Rupture, diseased spleen	2	4	0	0

Table III. *Diagnostic accuracy*

Admission diagnosis	*No. of cases*	*%*
Immediate rupture (38 cases)		
Diagnosis undetermined (ruptured spleen)	8	20
Missile wound, abdomen, chest, left	6	16
Diagnosis undetermined (intra-abdominal injury)	6	16
Multiple injuries, chest and abdomen	4	14
Diagnosis undetermined (surgical observation)	3	8
Traumatic rupture, spleen	3	8
Stab wound, abdomen and chest	3	8
Diagnosis undetermined (ruptured kidney)	1	2
Diagnosis undetermined (ruptured bladder)	1	2
Diagnosis undetermined (hematuria)	1	2
Fracture, left tibia and multiple left ribs	1	2
Hemopneumothorax, left	1	2
Delayed rupture (12 cases)		
Intracranial injury	4	35
Traumatic rupture, spleen	2	17
Diagnosis undetermined (ruptured spleen)	1	8
Diagnosis undetermined (contusion, abdominal viscus)	1	8
Diagnosis undetermined (myocardial infarction)	1	8
Puncture wound, abdominal	1	8
Contusions, chest and kidney	1	8
Hemopneumothorax	1	8

left hemidiaphragm were significant. As reflected in urinary findings, laceration or contusion of the left kidney was present in 14 per cent. Of patients with delayed rupture, head injury and rib fractures occurred in 33 per cent. Again, multiple fractures of ribs were present in many cases, the seventh rib (left) being the most commonly involved.

POSTOPERATIVE COMPLICATIONS

The most common postoperative complication in patients with immediate splenic rupture (Table VIII) was atelectasis of the left lung. Others included laceration of the tail of the pancreas, pneumonitis, and lower nephron nephrosis. Laceration of the tail of the pancreas, hemologous serum jaundice,

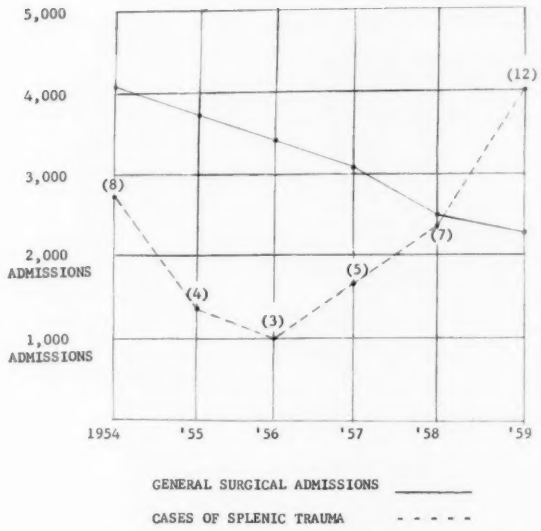

Fig. 2. Incidence of splenic trauma in general surgical admissions (neurosurgery and thoracic, plastic, and proctologic surgery admissions excluded).

Table IV. *Injuries causing splenic trauma*

Type	*No.*	*%*
Immediate rupture (38 cases)		
Auto accident (driving or passenger)	15	40
Gunshot wound, abdomen and lower chest (left)	6	16
Struck by moving vehicle (auto, etc.)	5	14
Fall (from tree, etc.)	4	11
Stab wound, lower chest (left) and abdomen	3	9
Ship collision (crew member)	1	2
Motorcycle accident	1	2
Struck with fist, left upper quadrant	1	2
Chest and abdomen struck by hoist aboard ship	1	2
Fall from moving car	1	2
Delayed rupture (12 cases)		
Auto accident (driving or passenger	5	44
Fall from tree	1	8
Struck by overturned tractor	1	8
Motorcycle accident	1	8
Struck with fist, left upper quadrant	1	8
Struck left flank on kitchen cabinet with considerable force	1	8
Ran into football goalpost	1	8
Severe coughing associated with cold (?)	1	8

Table V. *Leading complaints and physical findings*

Immediate rupture	*No. of cases*	*%*	*Delayed rupture*	*No. of cases*	*%*
*Complaints (33 patients)**			*Complaints (12 patients)†*		
Persistent, usually progressive abdominal pain and discomfort (generalized, 25, upper abdomen and LUQ, 8)	33	100	Persistent, usually progressive abdominal pain and discomfort (generalized, 8, upper abdomen and LUQ, 4)	12	100
Left shoulder pain	12	37	Sudden onset of severe complaints	6	50
Lower chest (left), pain and dyspnea	10	30	Left shoulder pain	5	41
Nausea and vomiting	4	12	Fainting and weak spells	4	33
Abdominal fullness	4	12	Lower chest (left), pain and dyspnea	3	25
Physical examination (38 patients)			Nausea and vomiting	3	25
Generalized abdominal rigidity and tenderness	28	74	Abdominal fullness	1	9
Rebound tenderness generally and referred to LUQ of abdomen	25	66	*Physical examination (12 patients)*		
Accelerated pulse (90+)	25	66	Abdominal rigidity and tenderness	12	100
Abdominal distention	12	32	Generalized rebound tenderness	9	75
Clinical shock (systolic BP less than 100 mm. Hg)	10	27	Abdominal distention, especially upper abdomen and LUQ	8	67
Hypoactive peristalsis	10	27	Accelerated pulse (90+)	6	50
Penetrating wound (chest, 4, abdomen, 5)	9	24	Clinical shock (systolic BP less than 100 mm. Hg)	7	58
Rectal examination (38 patients)			Hypoactive or absent peristalsis	3	25
No recorded examination	22	58	Palpation of mass in LUQ	4	33
Negative results	10	27		1	9
Diffuse tenderness	5	14	*Rectal examination (12 patients)*		
Fullness	1	2	No recorded examination	5	41
			Negative results	7	58

*Five patients were unable to recite complaints on admission.

†Complaints and physical findings occurred after latent period.

and urticaria secondary to blood transfusions occurred in 16 per cent of the patients with delayed rupture. One patient survived postoperative hemorrhage, hematoma, evisceration, and left subphrenic abscess, each of which required a surgical procedure.

MORTALITY RATE

In 54 patients, there were 7 deaths (Table IX). Five of the 52 who underwent operation died. From 1956 through 1959 26 patients underwent operation with no deaths. However, 1 patient with splenic trauma died shortly after admission to the emergency room (Table X, Case 22).

CASE REPORTS

Traumatic cyst of the spleen. The first patient was a 22-year-old sailor known to have had a mass in the left upper quadrant since an auto accident 2 years previously. After appropriate studies, surgical removal demonstrated it to be a large cyst of the spleen containing 1,800 ml. of fluid. The pathologic report was "cystic hematoma, spleen" (Figs. 3 and 4).

The second patient was a 30-year-old sailor who was found to have a mass in the left upper quadrant on admission for acute abdominal pain. Past history showed a similar episode approximately 1 year previously which had lasted for several days after a barroom brawl. Eventually an enlarged spleen was found on abdominal exploration. Pathologic report was "old traumatic cyst and recent subcapsular hemorrhage, spleen."

Rupture of the diseased spleen. The first patient was a 20-year-old sailor admitted with infectious mononucleosis who, after examination by 3 physicians, developed signs of splenic rupture. At operation a large, friable spleen was removed which showed subcapsular hemorrhage and rupture.

The second patient was a 22-year-old sailor admitted with infectious mononucleosis who had developed signs of splenic rupture after a bout of coughing and diarrhea. This was confirmed at operation. Both patients recovered (Figs. 5 and 6).

DISCUSSION

Wright and Prigot[13] in 1938 reported rupture of the spleen in 30 of 20,000 patients (or 1 in 666) admitted to the Traumatic Service of the Harlem Hospital. In 1950, Welch and Giddings[12] reported 200 cases of abdominal trauma, with 38 splenic injuries ranking second in occurrence to injuries of abdominal organs.

Zabinski and Harkins[14] found that 5 to 40 per cent of all traumatic splenic ruptures are of the delayed type with an average of 14 per cent.

Byrne[3] found that automobile accidents (passenger and pedestrian) were the chief agents of trauma in both immediate and delayed types and that abdominal pain was the most common symptom of traumatic rupture of the spleen. It occurred in 47 per cent, with shoulder pain (Kehr's sign) in 29 per cent, abdominal tenderness in 48 per cent, and abdominal rigidity in 41 per cent.

Although x-ray studies are usually of little value, Larghero[7] described 4 significant signs, (1) raised left hemidiaphragm, (2) displacement of the gastric shadow toward the midline, (3) subphrenic opacity (left), and (4) descent of the left part of the transverse colon.

Wright and Prigot[13] found that in 36 cases of splenic injury, fractured ribs were the most commonly associated, occurring in 10 instances, whereas fractures of other parts of the body (excluding ribs and skull) occurred in 8, injured kidneys in 6, and rupture of either diaphragm or bladder in 3. Hemopneumothorax occurred in 4 and a ruptured liver in 3. Roettig and associates[9] reported the most frequently associated injuries, in order, to be fractured ribs, hemothorax, fractures of extremities, injured kidney, ruptured liver, contusions of the pancreas, and retroperitoneal hemorrhage.

A comparison[13] showed that McIndoe had a mortality rate for traumatic rupture of the spleen of 27 per cent of 37 splenectomies, Hagen 46 per cent of 37, Lotsch 38 per cent of 138, Planson 37 per cent of 140, Johnson 31 per cent of 113, Connors 40 per cent of 25, and Wright and Prigot 23 per cent of 22. The principal causes of death were shock, peritonitis, and pulmonary hemorrhage. Byrne[3] reports 101 cases with a mortality rate of 17 per cent. The causes were multiple perforation of the gastrointestinal tract, fractures with shock, head injury, and, in 1 case, an unrecognized tear in the jejunum.

According to Schwartz[10] the first traumatic splenic cyst was discovered by Andral while he was performing an autopsy in 1829. The

Table VI. *Other diagnostic aids*

Routine chest and abdominal x-ray findings	*No.*	*%*
Immediate rupture (38 cases)		
Not significant	23	61
Distention of small and large intestines	5	14
Suggestive mass in LUQ	4	11
Evidence of free intraperitoneal fluid	4	11
Left hemidiaphragm elevated	3	8
Displacement of stomach medially (to right)	3	8
Splenic flexure of colon displaced inferiorly	2	5
Traumatic avulsion of superior portion of tenth rib, left	1	2
Stomach within the left hemithorax	1	2
Laboratory studies		
Hemoglobin below 10 Gm. on admission	10	27
Falling hemoglobin and hematocrit (within 24 hr.)	6	16
Elevated WBC (15,000 up)	17	45
Hematuria (gross, 4, microscopic, 15)	19	50
Delayed rupture (12 cases)		
Not significant	6	50
Displacement of stomach medially (to right)	4	33
Splenic enlargement	3	25
Depression inferiorly of splenic flexure of colon	2	16
Distention of small and large intestine	3	25
Left hemidiaphragm elevated	1	9
Laboratory studies		
Hemoglobin below 10 Gm. at onset of symptoms	5	41
Elevated WBC (15,000 up)	5	41
Hematuria (gross, 1, microscopic, 1)	2	16

Table VII. *Associated injuries*

Injuries	*No. of cases*	*%*
Immediate rupture (38 cases)		
None	15	40
Fracture, left ribs (multiple, 8; single, 3; eighth and ninth included in multiple fracture, 5; eighth included in fractures, 7)	11	29
Laceration, left hemidiaphragm	8	21
Fracture, extremities	5	14
Fracture, skull and face	3	8
Cerebral concussion	3	8
Hemothorax, left (alone)	4	11
Hemopneumothorax, left	5	14
Laceration or contusion of left kidney (nephrectomy required in 2)	5	14
Laceration, liver	3	8
Laceration, small bowel	1	2
Delayed rupture (12 cases)		
None	5	41
Head injury (including skull fracture)	4	33
Fracture, ribs (multiple, 3; eighth and ninth (left) included in multiple fracture, 1; seventh, left, included in fracture, 2)	4	33
Hemothorax, left	1	8
Hemopneumothorax, left	1	8
Penetrating wound, LUQ of abdomen	1	8
Fracture, extremities	1	8

first successful removal of a splenic cyst was by Pean in 1867. In 800 splenectomies only 4 cases were noted by Pemberton, an incidence of 0.5 per cent. From 1904 to 1940, 8 cases were found in the records of the Pathology Department at Bellevue Hospital. Between 1904 and 1934, 646 splenectomies, of which 2 were for hemorrhagic cysts, were performed at the Mayo Clinic.

Smith and Custer[11] emphasized the seriousness of splenic rupture in infectious mononucleosis by mentioning 4 deaths in 7 cases reviewed in 1946. At that time the Army Institute of Pathology had 44 cases coded as "spleen, spontaneous rupture." Infectious mononucleosis stood second as a cause (7 cases), exceeded only by recurrent malaria (22 cases). In January, 1959, Garfield and Gentry[5] found that 50 fatal cases of in-

Fig. 3. Diaphragmatic (convex) surface of splenic cyst. Note horn on inferior aspect of cyst. Lower extremity of splenic tissue remains intact as a tonguelike projection.

Fig. 4. Cut hilar surface of splenic cyst. Note marked trabeculation of cavity which contained 1,800 ml. of serous fluid.

Fig. 5. Convex (diaphragmatic) surface of the pathologic spleen. Arrow points to capsular tear with active and subcapsular hemorrhage. Note capsular tear superiorly.

Fig. 6. Convex surface of spleen cut into quadrants. Arrow points to site of active hemorrhage of lower extremity. Entire spleen is friable and mushy. Note thickness of subcapsular hematoma.

Table VIII. *Postoperative complications*

Type	*No. of cases*	*%*
Immediate rupture (36 patients)		
None	19	53
Atelectasis, left lung (base usually)	7	20
Laceration, tail of pancreas	5	14
Pneumonitis (left lower lobe, 3, bilateral, 1)	4	11
Lower nephron nephrosis (patients died)	3	9
Minor transfusion reactions (urticaria)	3	9
Abdominal wound dehiscence	2	6
Significant postoperative ileus (includes 1 dehiscence)	2	6
Abdominal wound infection	2	6
Subdiaphragmatic abscess	2	6
Massive pulmonary embolus (3 weeks postoperatively, patient died)	1	2
Septicemia (*E. coli*, patient died)	1	2
Delayed rupture (12 patients)		
None	3	25
Laceration, tail of pancreas	2	16
Urticaria secondary to blood transfusions	2	16
Homologous serum jaundice	2	16
Postoperative ileus (significant)	1	8
Streptococcal sore throat	1	8
Acute myocardial failure and pulmonary edema (patient died)	1	8
Evisceration, hemorrhage, hematoma, and left subphrenic abscess*	1	8

*Each required separate exploratory operation.

Table IX. *Total deaths from splenic trauma*

Date	*No. of cases*	*No. of deaths*	*Operation**
1949	1	0	Yes
1950	2	0	Yes
1951	1	0	Yes
1952	7	2	Yes (both)
1953	4	1	No
1954	8	2	Yes (both)
1955	4	1	Yes
1956	3	0	Yes
1957	5	1	No
1958	7	0	Yes
1959	12	0	Yes
Totals	54	7 (13%)	

*Total operations, 52. Postoperative deaths, 5. Operative mortality rate, 10 per cent.

Table X. *Summary of deaths*

Case no.	*Type of trauma*	*Clinical picture*	*Pathology of spleen*	*Multiple associated injuries*	*Principal causes of death*	*Time of death*
Immediate rupture						
2	Gunshot wound, RUQ of abdomen, exit left flank	Penetrating wound, RUQ of abdomen	Rupture of hilum	Lacerated abdominal aorta and liver, hemothorax (bilateral)	(1) Acute hemorrhage, (2) acute pulmonary edema, (3) lower nephron nephrosis	30 hr. postoperatively
4	Ship collision (crew member)	Shock on admission, 80/60, pulse 120	Macerated	Avulsion of testicle, multiple fractures and wounds	Lower nephron nephrosis	9 days postoperatively
12	Struck by auto	Unconscious, BP 40/20, pulse 100, first peritoneal tap negative, second showed gross blood	Laceration of hilum (bisected)	Head injury, fractured femur, multiple abrasions, lacerations	(1) Severe head injury, (2) hemoperitoneum	2 hr. after admission to emergency room
18	Auto accident	Excellent prior to sudden death	Lacerated hilum	Lacerated left hemidiaphragm, fractured pelvis and ribs (left)	Massive pulmonary artery embolus (3 wk. postoperatively)	3 wk. postoperatively
21	Stab wound of chest and left flank	Generalized abdominal tenderness and rigidity	Laceration of lower pole	Hemothorax (right), lacerated left kidney, colon	(1) Septicemia (*E. coli*) (2) lower nephron nephrosis, (3) atelectasis (bilateral)	9 days postoperatively
22	Auto accident (passenger)	Comatose, abdominal distention, 5 negative peritoneal taps, sixth positive for blood	Traumatic avulsion	Head injuries, multiple lacerations of liver, hemothorax (bilateral)	(1) Ruptured spleen, hemoperitoneum (3,000 ml.), (2) cerebral contusion	30 min. after arrival at hospital
Delayed rupture						
4	Tractor overturned, chest and upper abdomen crushed	Shock after enema, abdominal rigidity, rebound (2 wk. after accident)	Lacerated upper pole, massive subscapular hemorrhage	Brain concussion, fractured forearm and left ribs	(1) Acute myocardial failure, (2) acute pulmonary edema	2 hr. postoperatively

fectious mononucleosis had been reported. These cases were summarized by Liebowitz and 9 of the deaths were due to splenic rupture. Although rupture after abdominal palpation is commonly taught, Garfield and Gentry were able to find only one case in which this occurred.

CONCLUSIONS

1. During the past 10 years, splenic trauma has increased in incidence.

2. Splenic trauma may result in immediate rupture, delayed rupture, traumatic cyst, or rupture of the diseased spleen.

3. Trauma, combined with persistent abdominal pain, rigidity, rebound tenderness, rising pulse, and falling hematocrit, suggests splenic injury and presents a distinct indication for operation.

4. Established clinical shock in splenic trauma increases morbidity and death. Rapid and adequate treatment is mandatory!

5. Abdominal paracentesis is an unreliable diagnostic procedure which may lead to unnecessary delay.

6. Head injury, fractured ribs (left), abdominal rigidity, and a falling hematocrit demand consideration of acute or delayed splenic rupture.

7. Trauma and hematuria without demonstrable genitourinary damage (except to the left kidney) suggest splenic injury.

8. Splenic hemorrhage must be controlled rapidly after the abdomen is opened. Then, with accurate exposure, the spleen can be carefully removed and its intimately adjacent structures protected.

9. Vigorous palpation of the spleen in cases of infectious mononucleosis may change a medical curiosity into a surgical emergency.

10. Observance of basic postoperative principles is essential for rapid postsplenectomy recovery. Early ambulation and prevention of pulmonary complications is stressed.

11. Splenic trauma can cause death and complications with frightening ease. Splenectomy is a lifesaving operation when performed at the proper time. Truly, there is a golden period during which the diagnosis must be made and surgical treatment instituted to decrease the complications and possibility of death.

SUMMARY

Fifty-four cases of splenic trauma which occurred over a 10-year period are presented. They are classified as immediate and delayed rupture, traumatic cyst, and rupture of the diseased spleen. The total mortality rate was 13 per cent and the postoperative mortality rate 10 per cent. The increasing incidence, diagnosis, and operative problems are emphasized.

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Studies on direct-current coagulation

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Since 1951, members of our group have studied the relationship of potential differences and currents of injury to intravascular clotting. The experiments indicated that the blood-intimal interface across a blood vessel wall probably has a normal negative electric potential (of approximately 1 mv.) with respect to the adventitia.[5] Reversal of this potential difference often heralds intravascular occlusion.[5] Intravascular thrombosis with occlusion can be produced by surrounding an intact blood vessel with a very low voltage direct-current electric field. Clotting occurs about the positive electrode.[4, 9, 10] Coagulation of blood in vitro around the positive electrode of an electrode pair can be accelerated by use of a similar electric field,[4] while intravascular thrombosis can be delayed by wrapping an injured vessel with a negatively charged electrode.[3] Quantitation of the electrical energy necessary to produce intravascular thrombosis demonstrates that voltages and electric currents of the magnitude of injury potential differences and injury currents which occur in nature result in thrombotic occlusion of visualized vessels of the rat mesentery.[6, 7] The present communication concerns the early results of investigations of the potential utility of oriented low-voltage direct currents in the production of clinical hemostasis in organs difficult to suture or in situations in which the use of a high-frequency, alternating-current electrocautery is not applicable.

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METHOD

The electrical circuit consisted of a 24 v. battery in series with a milliameter and a variable resistance to control the total current flowing through the tissues which completed the circuit.[8] The negative electrode plate, wrapped with a towel wet with physiologic saline solution, was placed beneath the trunk. The positive platinum electrode was applied directly to the tissues to be rendered hemostatic. A positive-negative electrode dipole was used in some instances to coagulate a point source of bleeding, but appears less practical than the transcorporeal electrode applications. Successful direct current—induced hemostasis was produced in anesthetized rats, dogs, and human subjects.

ANIMAL EXPERIMENTS

The effect of the electrocoagulation technique was tested in rats by determining its ability to stop bleeding in the hemitransected liver. Several experiments were carried out in the dog including (1) electrocoagulation of one of paired incisions into the spleen or liver, (2) electrocoagulation of sites of injury by blunt instrument penetration of liver or spleen, (3) electrocoagulation of organ injuries in one of paired dogs with identical traumatic injuries to the same organ, and

(4) electrocoagulation of the hemitransected kidney. In all of the paired experiments, the nonelectrocoagulated injury site was untreated and served as the control. Currents of from 2 to 100 Ma. have been used in experimental animals.

CLINICAL TRIAL

In human subjects, the effectiveness of the technique in producing hemostasis has been evaluated in (1) fractured spleens, (2) liver injured by gunshot, (3) the bleeding surfaces of incisional wounds, (4) the bleeding prostatic bed during suprapubic prostatectomy, (5) pleural bleeding during intrathoracic operations, and (6) clamped incisional vessels. The technique has been used in 15 patients without determinable ill effects or sequelae. It is essential that the negative plate beneath the patient be covered with a cloth surface wet with saline to avoid areas of punctate skin burn. It is also mandatory that the positive pole of the battery be used for the electrocoagulation, since the negative pole has been shown to potentiate bleeding.

RESULTS

Animal experiments. In Table I the results of the paired experiments in rats and dogs are presented. The possibility that the difference in results between the control incisions and the electrocoagulated ones are due to chance is very small, as indicated in the last 2 columns. The experiments with hemitransected kidneys in the dog are not included in Table I. In 5 dogs, kidneys were incised through the long axis to the depth of the renal pelvis. In 2 dogs one kidney was transected and the contralateral kidney was used as the control. Hemostasis was obtained with direct current coagulation by compressing the two halves of the kidney against the positive electrode. The kidney was replaced within the abdomen after bleeding had stopped. In 3 dogs both kidneys were transected and electrocoagulated so that had the hemostatic technique resulted in loss of kidney function, the dog would have displayed evidence of renal insufficiency. All electrocoagulated transected kidneys continued to function. The amount of current required to produce hemostasis in the transected kidney was relatively large (30 to 35 Ma. for 10 minutes).

Clinical data. In patients the direct-current coagulation technique has been compared with the alternating-current electrocoagulation technique[1, 2] in the operating room to determine their comparative effectiveness and consequential comparative tissue destruction. The available evidence would indicate that direct-current electrocoagulation is not as rapid as the method of alternating-current electrocoagulation when applied to small "bleeders." However, direct-current coagulation is effective in causing hemostasis in diffusely bleeding surfaces, such as the apical pleura against which a laparotomy pad wet with physiologic saline solution has been applied. In such circumstances alternating-current electrocoagulation can be tedious and unnecessarily destructive.

In another application the positive coagulating electrode is thrust into a pool of

Table I

No. of animals	*Tissue*	*Polarity*	*Experimental wound*		*Control wound*		*P*	*Significance**
			No. of trials	*Hemostasis time (range in sec.)*	*No. of trials*	*Hemostasis time (range in sec.)*		
6	Rat liver	+	15	15-120	15	108-600	19.9	$1:10^{12}$
5	Dog liver	+	16	30-157	11	240-300	18.7	$1:10^{12}$
18	Dog spleen	+	40	12-275	16	90-300	14.4	$1:10^{12}$
12	Dog skin and subcutaneous vessels	+	38	4-180	10	15-300	16.6	$1:10^{12}$
8	Dog muscle	+	30	4-107	5	600-600	20.4	$1:10^{12}$

*Possibility that result is due to chance.

Table II. *Clinical use of direct current coagulation in thoracic procedures*

Patient	*Diagnosis*	*Operation*
F. DeJ.	Cavitary tuberculosis	Right upper lobectomy
J. K.	Persistent tuberculosis with bronchopleural fistula	Right lower lobectomy
M. M.	Mesothelial pleural cyst	Pleural cystectomy
M. R.	Empyema of chest	Decortication
R. B.	Residual (cavity) lung abscess	Segmental resection
R. B.	Empyema of chest	Decortication
W. C.	Residual tuberculosis cavity, right upper lobe	Right upper lobectomy
H. J.	Caseating tuberculosis, left upper lobe	Exploration of left upper lobe with dissection

Table III. *Clinical use of direct current coagulation in other areas*

Patient	*Diagnosis*	*Operation*	*Area coagulated*
B. C.	Benign prostatic hypertrophy	Suprapubic prostatectomy	Prostatic bed
C. R.	Benign prostatic hypertrophy	Suprapubic prostatectomy	Prostatic bed
N. S.	Esophagogastric gastric bleeding (gastric carcinomatosis)	Previous exploratory operation	Bleeding cancer within stomach
F. C.	Bleeding duodenal ulcer (preoperative diagnosis, esophageal varices)	None until bleeding continued	End of Sangstacken-Blakemore tube
A. J.	Liver injury (gunshot injury to liver)	Exploratory laparotomy	Stellate bullet wound in liver
I. B.	Splenic injury (fractured spleen)	Exploratory laparotomy	Spleen

*Unless otherwise specified.

Area coagulated	*Current (Ma.)*	*Time (min.)*	*Comments*
1. Incision	20-40	10 sec.-1 min.	
2. Apical parietal pleura	40	5	
3. Rib articulation	40	10	
1. Incisional bleeders	20-70	2	Unclamped artery
2. Intercostal vessels	70-80	5	
1. Incision	18	5 to 20 sec.	Clamped vessels
2. Bed of pleural cyst	18	3	Application through laparotomy pad
1. Incisional bleeders	20-22	5 to 20 sec.	Clamped vessels
2. Visceral pleura	40-80	3	Through laparotomy pad saturated with (0.9%) NaCl
1. Apical pleura, generalized ooze	60	10	Through saline-wet laparotomy pad
1. Incisional bleeders	25	15 sec.-1 min.	Clamped vessels
2. Diaphragmatic		4	
3. Thoracic pleural artery		1	Clamped vessels
1. Apex of pleural cavity	30	6	Hemostatic through laparotomy pad
1. Parietal and visceral pleura	40-60	5	Several areas coagulated
		10	
		17	

Current (Ma.)	*Time (min.*)*	*Results*	*Comments*
30	5	Hemostatic	Secondary hemorrhage minimal sixth postoperative day
30	10	Hemostatic	Prostatic bed capsular bleeding
5	2 hr.	Hemostatic	Stomach contained 3,000 ml. gastric fluid
20	1 hr.		
30	20		After stomach emptied 14 hours later
30	30	No hemostasis	Electrode within cardia of stomach too far from bleeding duodenal ulcer, no evidence of tissue injury at operation
35	30		
20	1 hr.		
20	2.5	Partial hemostasis, hemostatic	Period longer than 2 min. necessary to obtain hemostasis
50	2.0		
20	5	Partial hemostasis	During early operation moderately effective
60			

blood at the bleeding source and is held in place by a laparotomy pad until hemostasis occurs. Direct-current electrocoagulation is less effective with high-pressure blood vessels greater than 1 mm. in diameter; however, these can be clamped and ligated separately. Tables II and III summarize the results with the technique in the first 14 patients. The technique was effective in all cases except as indicated.

CASE REPORT

S. N., a 62-year-old man, underwent exploratory operation for a massive inoperable carcinoma of the stomach on Feb. 10, 1960. He had been anemic preoperatively and had required 3 pints of blood. Eight days after operation he was sent home, only to return in 6 days with a hemoglobin concentration of 4 Gm. per cent, guaiac positive stools, and coffee-ground gastric aspirate. Transfusions were followed by additional bleeding until his blood type (B Rh positive) become unobtainable. We were asked to see the patient to determine if the use of the direct-current coagulator might aid hemostasis. A platinum electrode loop was threaded down a Levin tube and braided over the end. The electrode was positioned in the stomach by means of the fluoroscope. The loop was then attached to the positive pole of the electrocoagulator. The negative electrode, attached to a metal plate wrapped in a saline-wet towel, was placed beneath the conscious patient. The stomach contained considerable fluid which was allowed to remain in place. A current of 5.0 Ma. was passed for 2 hours. The stomach was then nearly emptied, and the aspirated material was guaiac positive. An additional current of 20 Ma. was passed for 15 minutes. Removal of all residual gastric content showed that the guaiac test was now minimally positive. The Levin tube with its attached platinum electrode was left in place. On the following day, though gastric aspirate was guaiac negative, a 30 Ma. current was passed for 20 minutes, the stomach contents drained, and the electrode tube removed. Stools and gastric aspirate remained guaiac negative thereafter for 3 weeks.

PATHOLOGY

Examination of the animal tissues through which the current has been passed showed little histologic evidence of tissue damage. Cells directly beneath the positive electrode, to a depth of 4 to 5 cell layers only, appeared crenated. No other morphologic evidence of damage could be seen. The blood which had puddled beneath the positive electrode demonstrated histologic evidence of clotting. These findings are in contrast to the tissue changes seen after alternating-current electrocoagulation, when the radius of injury is sometimes as much as 1 cm. from the point of electrode application.

DISCUSSION

The technique of direct-current coagulation appears to be more satisfactory for hemostasis in certain situations than does high-frequency alternating-current electrocoagulation. The technique described can be used when uncontrolled bleeding occurs by thrusting the electrode into an accumulating pool of blood. The pool of blood itself acts as the positive electrode in this situation. Alternating current can cause coagulation of the pool only by electrodesiccation. Application of the described technique has therefore been found to be selectively useful in controlling the oozing from raw surfaces of liver, spleen, kidney, pleura, stomach, and prostate. In these situations ligation of bleeding points is not practical, and alternating current electrodesiccation is not effective and may be contraindicated because of its destructive effect.

We are not certain that the technique represents augmentation of the normal physiologic process of coagulation. However, the available information gives evidence that the positive electrode adds energy to the clotting process so that the blood thromboses at a faster rate than normal.[1-7] It is possible that direct-current electrocoagulation may be useful in brain surgery and in operations on patients with blood dyscrasias and a bleeding tendency. We are at present investigating both of these areas of potential usefulness.

SUMMARY

Experiments with the positive electrode of an electrode pair attached to a battery as a low-voltage, direct-current source to create hemostasis in tissues has been described. Results indicate that positive-pole, direct-current electrocoagulation is effective in creating hemostasis in tissues not easily

sutured or electrodesiccated. Currents of up to 100 Ma. have been passed in the living animal without visible untoward results. The results both in experimental animals and in clinical use are briefly presented and appear to be promising.

We wish to thank Dr. E. E. Suckling for his helpful suggestions, Mr. James Murphy for his help with the design and construction of the first models of the direct-current electrocoagulator, and to Dr. Gordon Hennigar for his help in preparing the histologic sections of the tissue specimens.

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Studies by electron microscope on various forms of induced cardiac arrest in dog and rabbit

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Previous investigations by one of us[6] have shown light, microscopic regressive muscular changes in the right ventricle of canine hearts which had been perfused over a period of 45 minutes and longer from the coronary sinus. During this procedure the right ventricle is practically anoxic and consequently the histologic findings have been interpreted as due to the lack of oxygen. At present the limiting time factor involved in the tolerance of the heart to anoxia is unknown.

In open-heart surgery various forms of cardiac arrest have been utilized. Undoubtedly the use of cardioplegic agents has facilitated the accurate closure of inaccessible ventricular septal defects. However, postoperative functional disorders of cardiac activity and, furthermore, late regressive histologic changes found at autopsy in hearts which had been arrested should not be disregarded according to Allen and Lillehei.[1] They warned that potassium arrest should be avoided by all means in hearts with extensive myocardial damage or low myocardial reserve. In any kind of induced cardiac arrest anoxia is probably the common factor which causes hazards to patients operated upon for cardiac anomalies.

The present studies have been carried out with the electron microscope to ascertain the early effects of various forms of induced cardiac arrest on the ultrastructures of the cardiac muscle cell in dogs and rabbits.

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MATERIAL AND METHODS

Mongrel dogs and rabbits were anesthetized with Pentothal sodium (30 mg. per kilogram of body weight intravenously). After endotracheal intubation the animals were ventilated by means of a mechanical insufflation apparatus. Some animals were cooled by immersion in a bath of ice water. The thoracotomy was carried out through a midline incision. The venae cavae were dissected free and the azygos vein was ligated. In the experiments with the pump oxygenator (Lillehei-DeWall), the left femoral artery was utilized for the return of oxygenated blood via a No. 13 polyethylene tube. In all experiments continuous electrocardiographic tracings were made throughout. In some animals arterial pressure was monitored by means of a catheter introduced through the right femoral artery into the aorta and connected to a pressure gauge (Schwartzer) for recording on the Cardioscript apparatus (Schwartzer).

After inflow occlusion and venting of the heart by means of small incisions made in the left and right atrial pouches, the root of the aorta was clamped. With this procedure, cardiac arrest was induced in 4 different categories of experiments.

In Category A, 6 experiments were conducted with normal body temperature. In Category B, 2 experiments were carried out

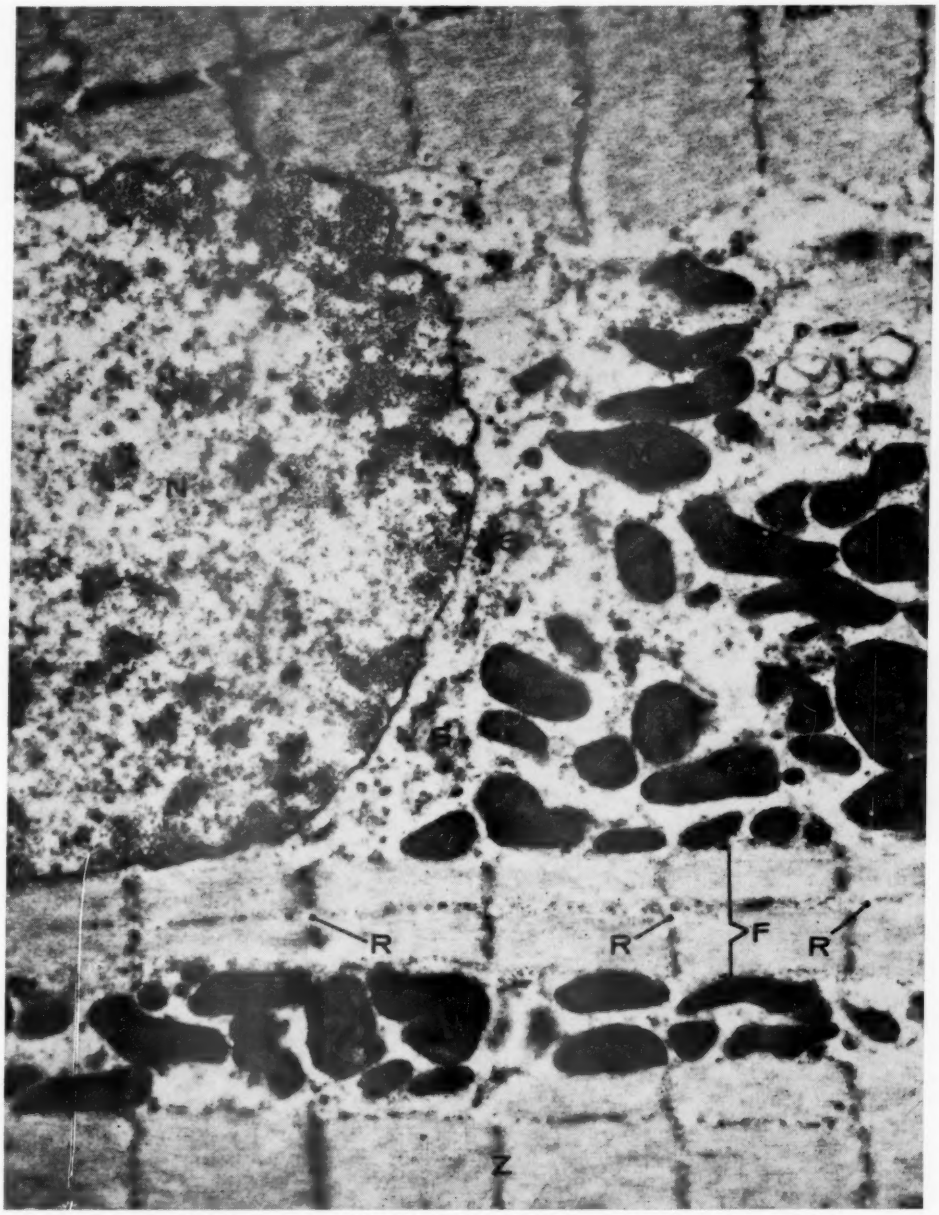

Fig. 1. Normal rabbit myocardium. Mitochondria *(M)* are densely filled with cristae and arranged in rows between the myofibrils *(F)* in the long axis of the muscle. Numerous mitochondria, Golgi apparatuses *(G)* and sarcoplasmic reticulum *(R)* are noted at the poles of the nucleus *(N)*. Within the myofibrils the z-bands *(Z)* are distinctly visible. Sarcoplasmic reticulum is most conspicuous at the level of Z-bands. (×20,000; reduced ⅓.)

with a body temperature of 35° to 36° C. during perfusion of the animal with the pump oxygenator. Category C consisted of 3 experiments with the body temperature at 18° and 22° C. In Category D, 8 experiments were performed with normal body temperature and injection of potassium or sodium citrate solution (2.5 and 25 per cent, undiluted and diluted with the animal's own blood) into the root of the aorta proximal to the clamp just above the orifices of the coronary arteries.

For electron microscopy, samples of cardiac muscle of the left ventricle taken at different time intervals were fixed in 1 per cent osmium tetroxide solution buffered

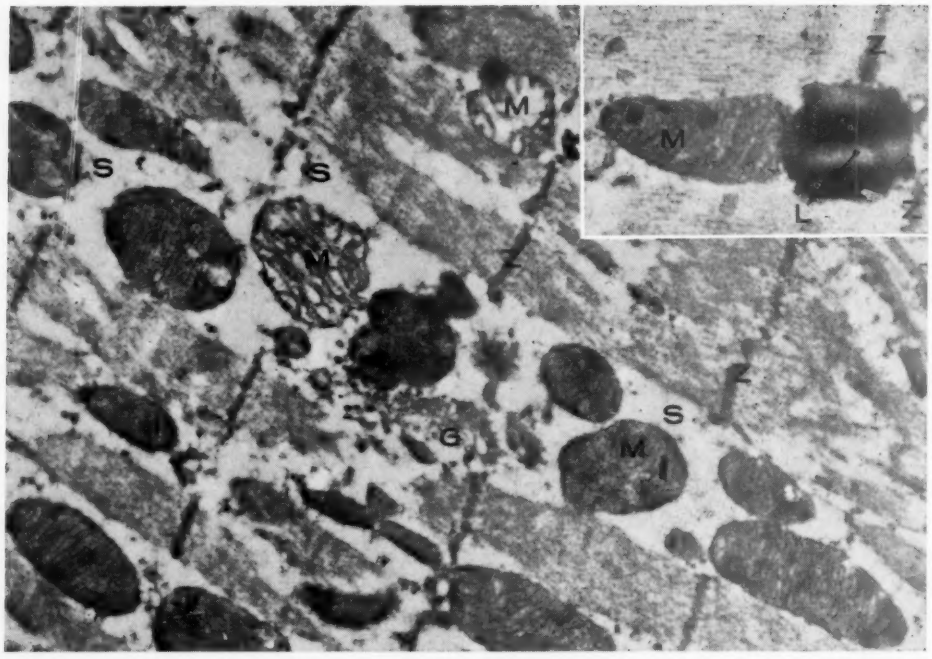

Fig. 2. Dog myocardium after anoxia for 30 minutes at a body temperature of 37.5° C. Mitochondria *(M)* show a clumping of the cristae and vesiculation. Interfibrillar space *(S)* is widened. There are patchy light areas within the myofibrils and random indistinct z-bands *(Z)*. There are no conspicuous changes in the sarcoplasmic reticulum. *G*, Golgi apparatus. (×25,000; reduced ⅕.) The inset shows rabbit heart after anoxia for 30 minutes. Lipid bodies *(L)* are adjacent to the mitochondria *(M)*. (×30,000; reduced ⅕.)

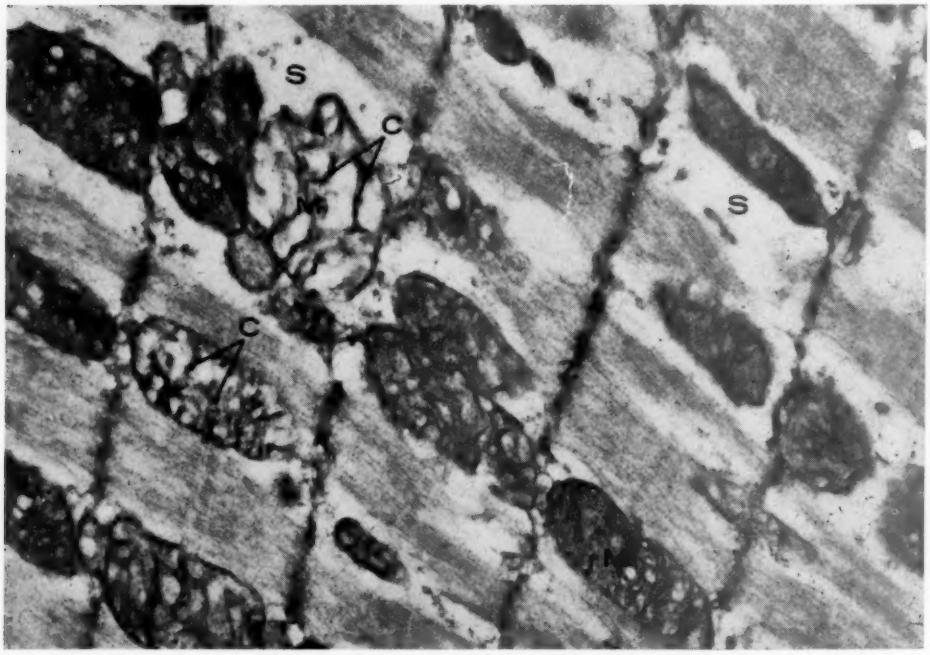

Fig. 3. Dog myocardium after anoxia of 30 minutes and 3 hours after perfusion with pump-oxygenator. There is profound vesiculation of mitochondria *(M)*. *C*, Cristae; *S*, interfibrillar space; and *Z*, z-band. (×25,000; reduced ⅕.)

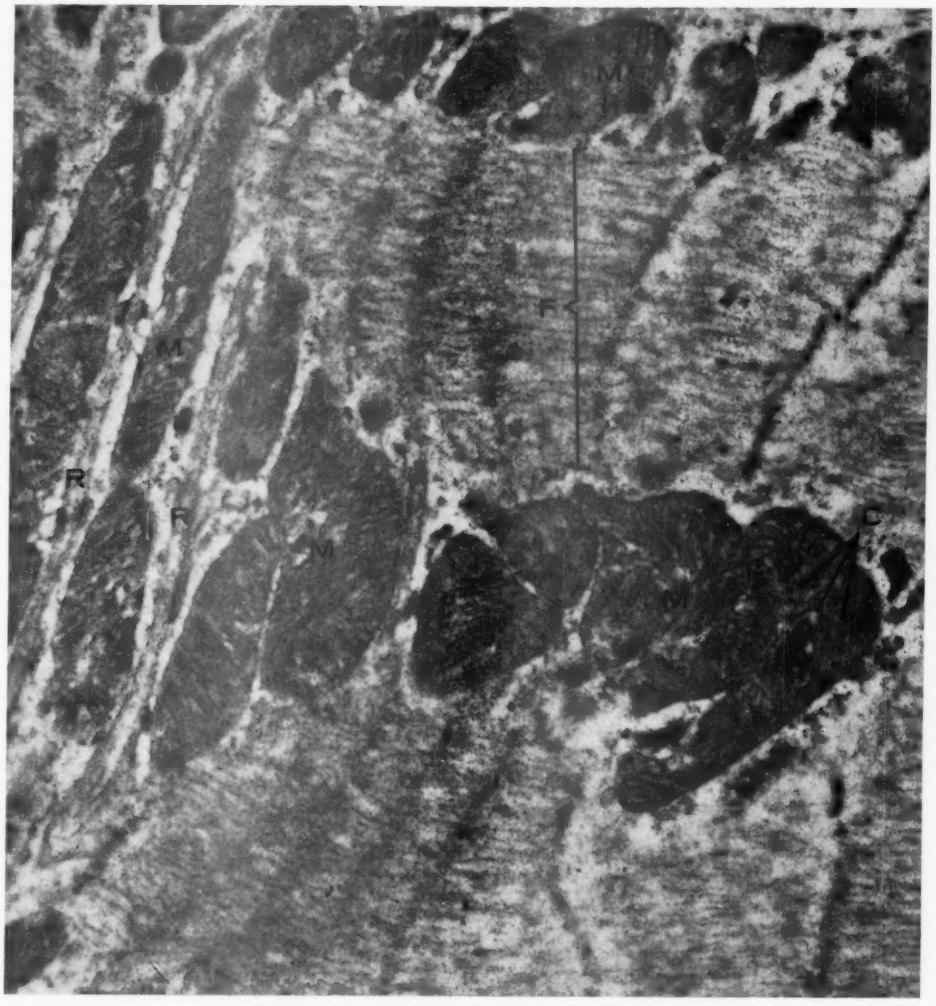

Fig. 4. Dog myocardium after anoxia of 45 minutes at a body temperature of 18° C. Mitochondria *(M)* are unchanged and there is no widening of the interfibrillar spaces. *R,* Sarcoplasmic reticulum; *F,* myofibril; *Z,* z-body; and *C,* cristae. (×30,000; reduced ⅕.)

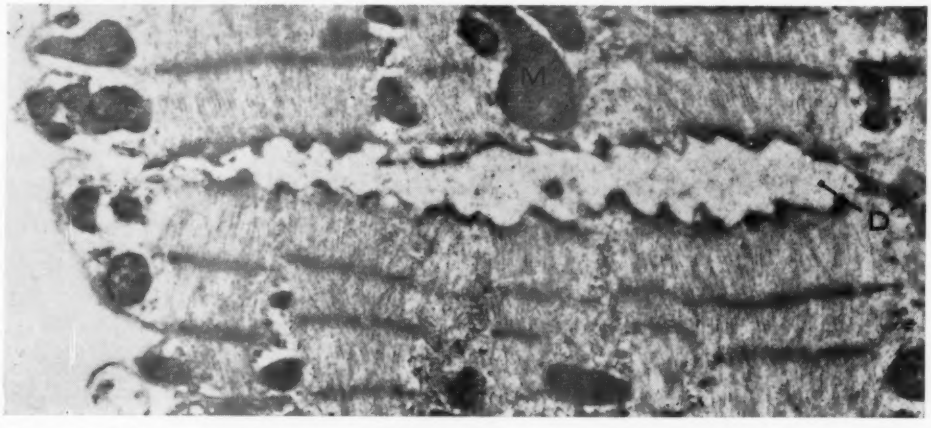

Fig. 5. Rabbit myocardium. Undiluted 25 per cent potassium citrate was used. There is marked widening of the space and distortion of the zig-zag intercalated discs *(D). M,* Mitochondria. (×17,500; reduced ⅙.)

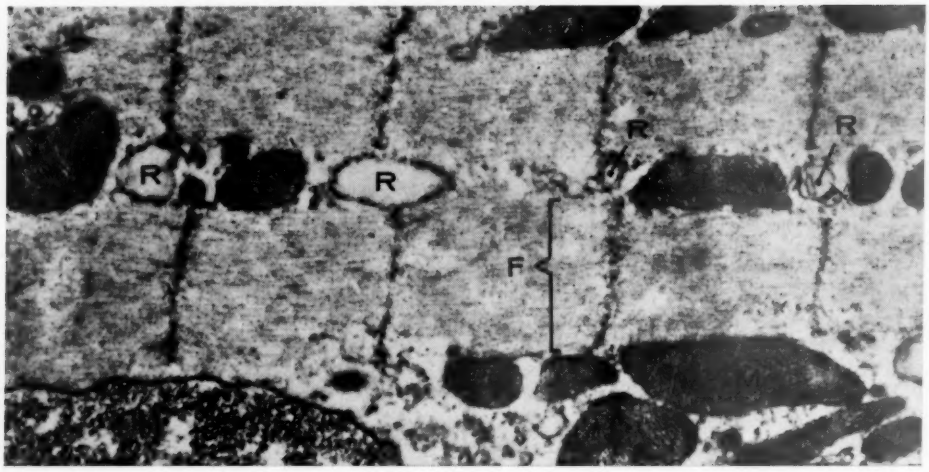

Fig. 6. Same heart as in Fig. 5. There is conspicuous ballooning of the sarcoplasmic reticulum *(R)* at the level of z-bands. Mitochondria *(M)* are not affected. *N*, Nucleus, and *F*, myofibril. (×25,000; reduced 1/6.)

with Veronal acetate at pH 7.42. Saccharose was added to the fixative. The fixed samples were embedded in a mixture of butyl and methyl methacrylate, the ratio of which was 20 to 80. They were cut with a glass knife on a Porter-Blum and Sjöstrand microtome. The observations were made with an electron microscope (Zeiss, type EM 8-II) at 40 to 50 kv.

RESULTS

The ultrastructure of the myocardium of the rabbit and dog heart has been described by several investigators.[7, 8, 11, 12]

For comparison, a section of a normal rabbit heart is illustrated in Fig. 1. The rabbit and the dog heart show essentially the same arrangement of the fine structures of the myocardial cell. Changes attributable to the anesthesia or surgical manipulation have not been noted.

Fig. 2 demonstrates the effect of anoxia on the dog heart under normothermic conditions. There is a distinct increase in space between the myofibrils and the normally densely packed mitochondria at the poles around the nucleus. The mitochondria are moderately enlarged and swollen. Vacuolation with loss of the matrix and separation of the clumped cristae are noticeable. These changes within the mitochondria occur as early as 10 minutes after anoxic conditions have been established. At several sites on the section, indistinct z-bands and patchy, optically empty areas within the myofibrils are visible which suggest regressive changes of the myofilaments. The sarcoplasmic reticulum does not show any conspicuous changes. Scattered lipid bodies located close to the mitochondria have been observed in the late stages of anoxia.

In the rabbit heart the changes described for the dog heart have been the same except that an increased formation of lipid bodies has been noted. They appear as early as 10 minutes after the induction of anoxia and increase in number with the duration of anoxia. The lipid bodies are so closely adjacent to the mitochondria that no space between the structures can be distinguished (Fig. 2, inset).

Fig. 3 shows the section of a heart of a dog which had been perfused with the pump oxygenator while the aorta was clamped over a period of 30 minutes. The dog died 3 hours after the perfusion. The body temperature during the perfusion was between 36° and 35° C. Profound vesiculation of the mitochondria will be noted.

Under hypothermic conditions, even after 45 minutes of anoxia, the structure of the mitochondria is unchanged (Fig. 4).

Injection of potassium citrate causes changes in the myocardial cell which are

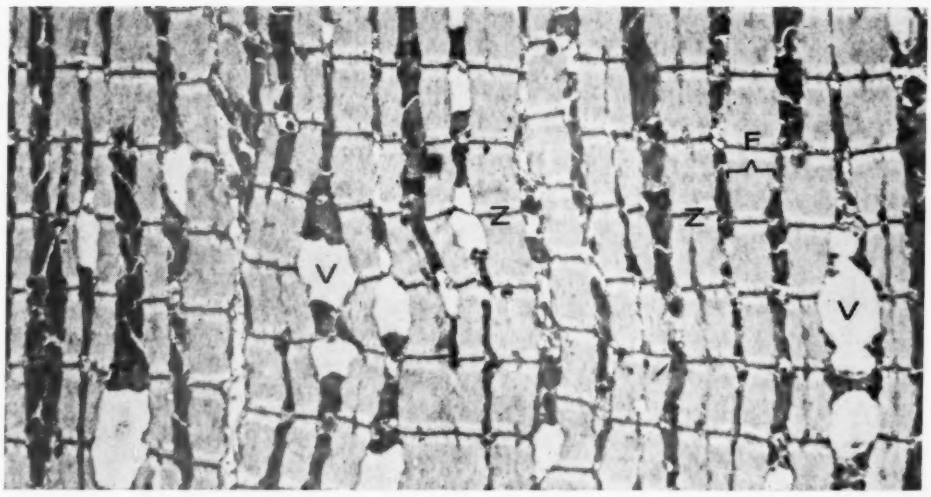

Fig. 7. Same heart as in Fig. 5. Large vacuoles *(V)* between the myofibrils *(F)* are seen. *Z*, Z-bands. (×6,000; reduced ⅙.)

quite different from those which occur in the anoxic heart. Alterations were most pronounced when undiluted 25 per cent potassium citrate was injected. As may be seen in Fig. 5, the intercalated discs, that is, the lines of end-to-end attachment between longitudinally arranged muscular fibrils, are distorted. A distinct ballooning of the sarcoplasmic reticulum is quite pronounced at the level of the z-bands, whereas the mitochondria appear unchanged (Fig. 6). Large vacuoles between the myofibrils are visible (Fig. 7). The myofibrils are not sharply defined. After injection of diluted 25 per cent or 2.5 per cent potassium citrate a ballooning of the sarcoplasmic reticulum and an interfibrillar formation of vacuoles are noted, although to a lesser degree than when undiluted potassium citrate has been given. The mitochondria and the intercalated discs are apparently unaffected (Fig. 8). The changes in the sarcoplasmic reticulum are essentially the same after injection of sodium citrate (Fig. 9).

DISCUSSION

As has been described by other investigators,[3, 9, 10] distinct and consistent morphologic changes in cardiac muscle can be seen as early as 10 minutes after induction of anoxia. The mitochondria are apparently affected earliest and most conspicuously. They are enlarged, probably because of an increase in the amount of fluid. Lipid bodies appear in the rabbit heart in the early stages of anoxia and increase in number with the duration of ischemia of the heart. The accumulation of lipid bodies in the immediate vicinity of the mitochondria would give a morphologic parallel to the biochemical findings concerning oxidation of fatty substances within the mitochondria.[4] During anoxia, when the function of the mitochondria is interfered with, the fatty material remains unoxidized and may thus appear in the form of lipid droplets in the neighborhood of the mitochondria.

Our observation that in the beating heart the histologic changes progress at a faster rate than in the arrested heart suggests a more intense accumulation of acid metabolites such as lactic acid, pyruvic acid, and so forth, due to the contractions of the myocardial fibers. This reasoning is supported by investigations of Bentall and Melrose.[2] As anticipated, our finding of unaltered mitochondria under hypothermia even after 45 minutes of myocardial anoxia lends support to the biochemical studies of Fleckenstein and colleagues[5] on cardiac metabolism of energy-rich phosphates.

Most interesting to us have been the histologic changes in hearts arrested by potassium or sodium citrate. The mitochon-

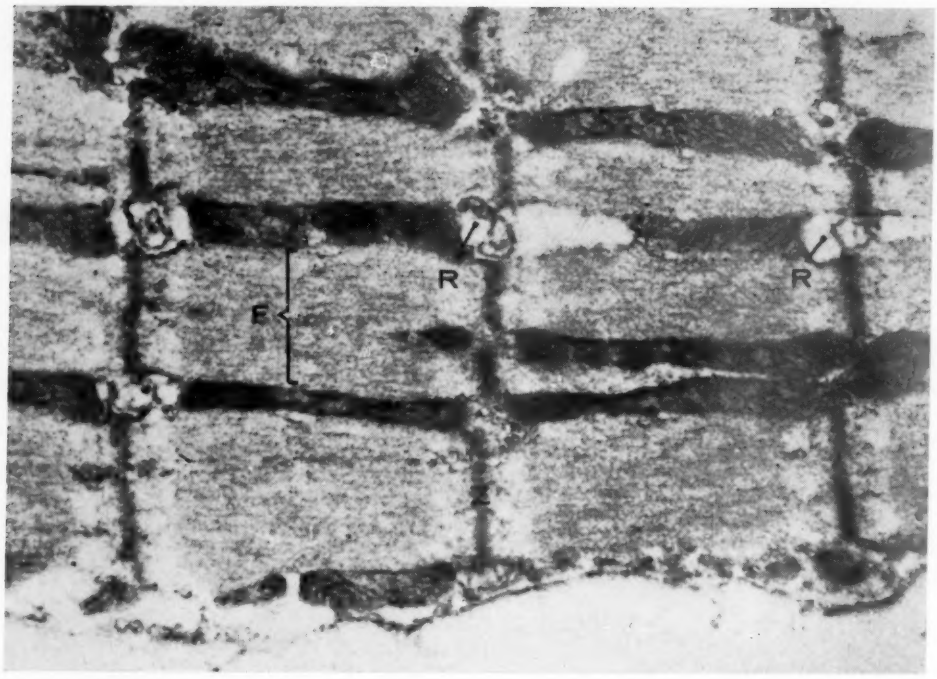

Fig. 8. Rabbit myocardium. Potassium citrate (2.5 per cent) diluted with blood was used. Mitochondria *(M)* are unaffected. There is distinct ballooning of the sarcoplasmic reticulum *(R)* near the z-bands *(Z)*. *F*, Myofibrils. (×32,000; reduced ⅕.)

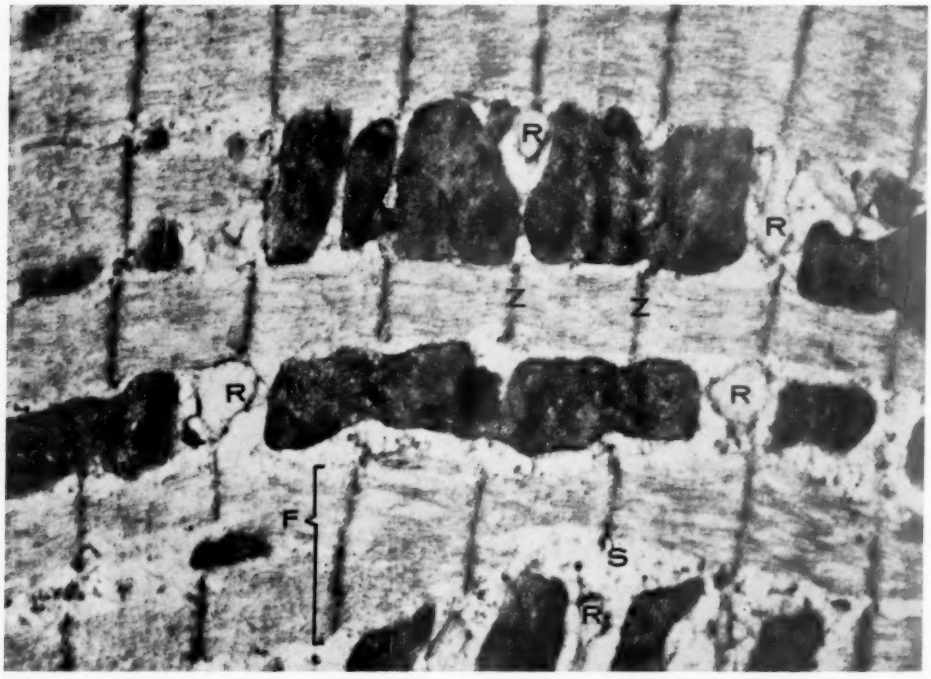

Fig. 9. Rabbit myocardium. Sodium citrate (2.5 per cent) diluted with blood was used. As in Fig. 8, ballooning of the sarcoplasmic reticulum *(R)* is visible. There are no changes in the mitochondrial structure *(M)*. *F*, Myofibril; *S*, interfibrillar space; and Z, z-band. (×25,000; reduced ⅕.)

dria appear to be unaltered. However, profound changes occur in the sarcoplasmic reticulum. Apparently this structure is important in electrical conduction. The observations reported here appear to give histologic evidence of this concept. Since sodium citrate had a similar, although not as pronounced, effect as potassium citrate on the sarcoplasmic reticulum of the myocardial cell, the calcium ion concentration or rather the calcium/potassium/sodium ratios seem to play the decisive role in the conduction of impulses to the myocardium. At this point it remains open to speculation whether or not the puffy appearance of the sarcoplasmic reticulum is due to an imbibition with fluid caused by a change in the ionic concentration within the sarcoplasmic reticulum.

SUMMARY

1. Under normothermic conditions anoxia causes a swelling and vacuolation of the mitochondria, the cristae of which are clumped. Patchy, optically empty areas within the myofibrils are recognized. Lipid bodies adjacent to the mitchondria appear to be more numerous in the anoxic rabbit heart than in the dog heart. No changes of the mitochondrial structure have been observed with hypothermia after 45 minutes of anoxia.

2. Injection of undiluted or diluted potassium or sodium citrate produces ballooning of the sarcoplasmic reticulum and apparently has no effect on the structure of the mitochondria. The significance of these findings in relation to the mechanism of conduction of impulses to the myocardium has been discussed.

The authors wish to thank Dr. F. Linder for the provision of facilities in his laboratory and Dr. W. Schwarz for his invaluable aid and advice in electronmicroscopy. The skillful technical assistance of Mr. V. Fehr in the experiments is gratefully appreciated.

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The surgical correction of endocardial cushion defects

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Progress in surgery has stimulated interest in and ever-increasing understanding of the anatomic and embryologic aspects of anomalies which result from the incomplete development of the atrioventricular canal. Unfortunately, a confusing nomenclature has appeared in the literature.[7, 10, 12] However, as the basic abnormality common to each variety results from the defective development of the endocardial cushions, the term "endocardial cushion defects," proposed by Watkins and Gross,[13] appears to be most appropriate.

EMBRYOLOGY

Early in the fifth week of development, the fetal heart consists of a single atrium and a single ventricle. These 2 chambers are connected by an undivided channel, called the atrioventricular canal, formed by a constriction in the wall of the heart tube (Fig. 1, *a*).

Division of the common atrium by the primary atrial septum, the ventricle by the ventricular septum, and the common atrioventricular canal by the dorsal and ventral endocardial cushions then begins.

The endocardial cushions eventually fuse to divide the once-common atrioventricular canal into a left half (the mitral orifice) and a right half (the tricuspid orifice). The endocardial cushions are masses of tissue which not only have anterior and posterior dimensions, but also extend cephalad, caudad, to the left, and to the right for some distance.[12] Therefore, in addition to dividing the common atrioventricular canal, they contribute toward the division of the common atrium and common ventricle, and to the formation of the atrioventricular valves. The left extensions fuse to form the anteromedial leaflet of the mitral valve, and the right extensions form the septal leaflet of the tricuspid valve. The cephalad extension fuses with the inferior margin of the primary atrial septum and the caudad extension develops into the posterior part of the membranous ventricular septum (Fig. 1, *b*).

Failure of the endocardial cushions to develop and fuse centrally can thus result in a variety of congenital cardiac anomalies involving the atrioventricular valves and the adjacent portions of the atrial and ventricular septa. Indeed, Kiely and his associates[6] postulated 14 theoretically possible combinations of defects.

CLASSIFICATION OF DEFECTS

There is no objection to the anatomic classification suggested by Wakai and Edwards[12] and by Campbell and Missen.[4] From the practical standpoint, however, only 2 groups need be considered, (1) endocardial cushion defects without ventricular septal defects and (2) endocardial cushion defects with ventricular septal defects.

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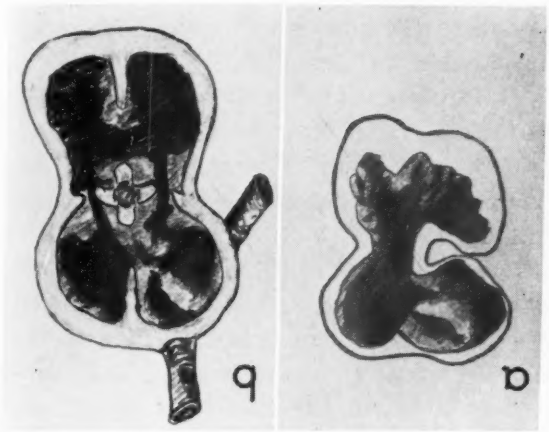
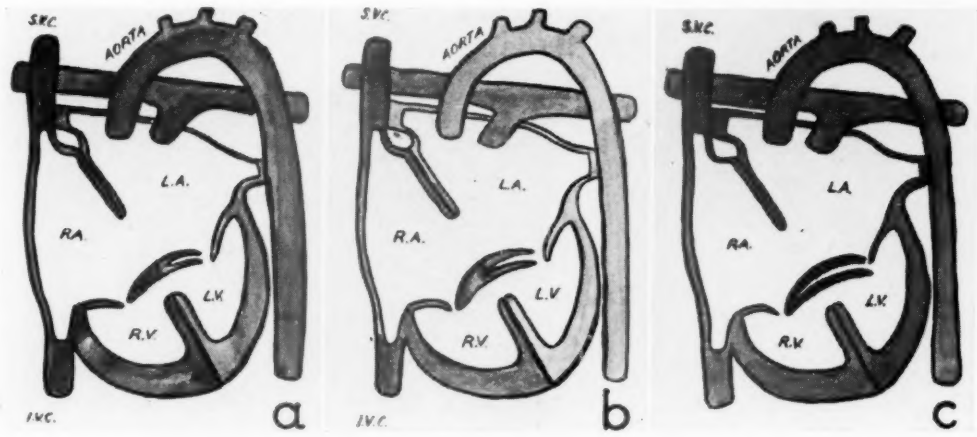


Fig. 1. *a*, Drawing which shows the single atrium and single ventricle connected by the undivided atrioventricular canal in the human fetal heart. *b*, Drawing which shows the growth of the primary interatrial septum and muscular interventricular septum and the various components of the endocardial cushions.

Endocardial cushion defects without ventricular septal defects. In this group, although there has been incomplete development of the middle and cephalad portions of the endocardial cushions, the caudad projection has developed normally to complete the formation of the ventricular septum. There is incomplete division of the atria and varying degrees of incomplete development of the anteromedial leaflet of the mitral valve and septal leaflet of the tricuspid valve, but no anatomic ventricular septal defect.

The defects in atrial septation may vary from complete absence of the atrial wall—single atrium[8]—to partial absence of the septum—the so-called ostium primum defect. In addition, there is incomplete fusion of the portions of the ventral and dorsal endocardial cushions which form the anteromedial leaflet of the mitral valve and sometimes the septal leaflet of the tricuspid valve.



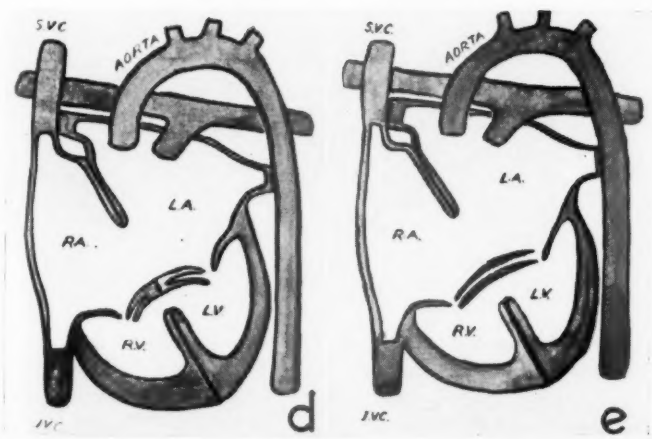


Fig. 2. Endocardial cushion defects without ventricular septal defects. The drawings show various defects of the mitral and tricuspid valves which result from the incomplete fusion of the endocardial cushions.

This area constitutes the lower margin of the atrial septal deficiency.

The anatomy of this section of the anomaly varies and, as a clear understanding is of utmost importance in the correct surgical treatment of the defect, this will be discussed in greater detail.

Incomplete cleft of the anteromedial leaflet of the mitral valve. Although the peripheral portion of the anteromedial leaflet of the mitral valve is cleft, the base has developed and is attached, with the base of the normally developed septal leaflet of the tricuspid valve, to the top of the fully developed ventricular septum (Figs. 2, *a,* and 3, *a*).

Complete cleft of anteromedial leaflet of the mitral valve. The lower edge of the atrial septal defect is usually formed by the intact base of the septal leaflet of the tricuspid valve base, fused to the top of a fully developed ventricular septum. The anteromedial leaflet of the mitral valve is completely cleft up to this base (Figs. 2, *b,* and 3, *b*).

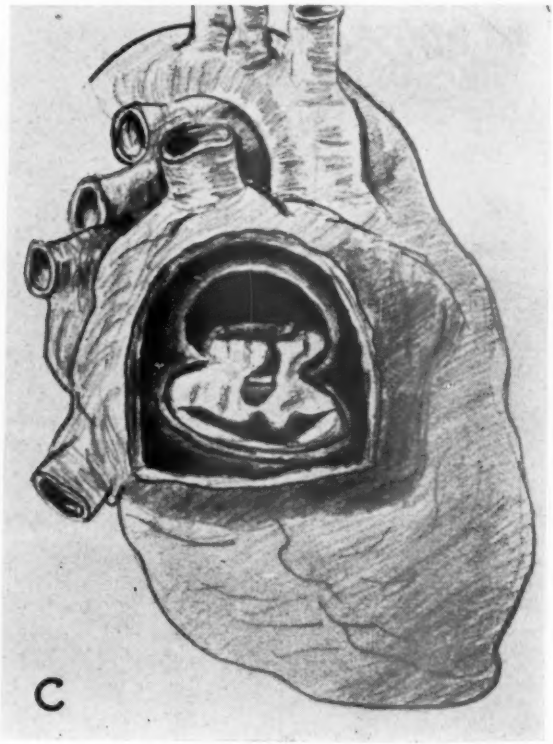


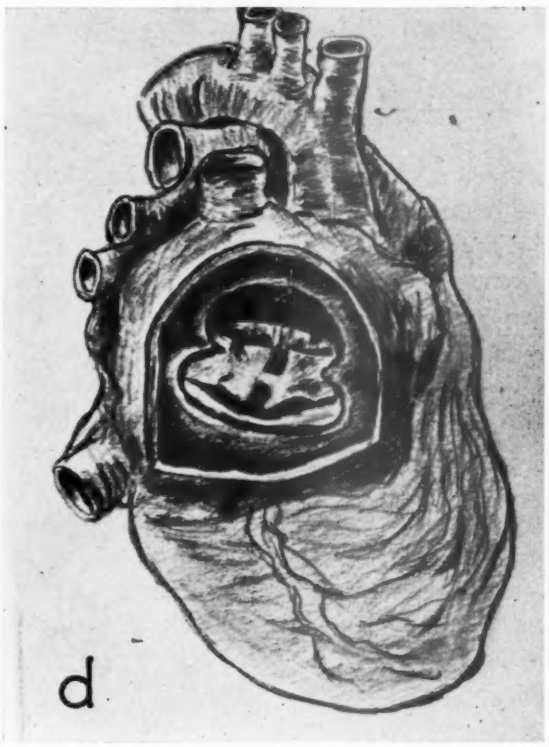
Fig. 3. Endocardial cushion defects without ventricular septal defects. The drawings show the anatomy of various defects in the atrioventricular valves as seen from the right atrium. *a,* Incomplete cleft of anteromedial leaflet of mitral valve. *b,* Complete cleft of anteromedial leaflet of mitral valve. *c,* Complete cleft of anteromedial leaflet of mitral valve and incomplete cleft

Complete cleft of anteromedial leaflet of mitral valve and incomplete cleft of septal leaflet of tricuspid valve. In these cases the periphery of the tricuspid valve may not be cleft, although the anteromedial cleft appears to extend a few millimeters into the base of the septal leaflet, leaving a segment of the upper border of the normally developed ventricular septum bare (Figs. 2, *c*, and 3, *c*).

Incomplete cleft of anteromedial leaflet of mitral valve and of septal leaflet of tricuspid valve. These defects are characterized by clefts not only of the anteromedial leaflet of the mitral valve, but also of the septal leaflet of the tricuspid valve. However, there is a narrow bridge of valvular tissue which joins the anterior half with its respective posterior half, and this bridge of valvular tissue is fused to a normally developed ventricular septum—the transitional form[12] (Figs. 2, *d*, and 3, *d*).

Complete cleft of anteromedial leaflet of mitral valve and of septal leaflet of tricuspid valve. Although a continuous cleft extends across the anteromedial leaflet of the mitral valve and septal leaflet of the tricuspid valve, the ventricular septum is fully developed. We believe that these anomalies should not be grouped under the heading of "complete atrioventricular canal." As the surgical repair does not include the closure of a ventricular septal defect, the prognosis is much better than in cases of deficient development of the ventricular septum (Figs. 2, *e*, and 3, *e*).

Endocardial cushion defects with ventricular septal defects. Under this heading are grouped anomalies which result when, in addition to varying degrees of malformation of the middle and cephalad portions of the endocardial cushions, there is also incomplete development of the caudad extension. There is thus always a deficiency in the top of the ventricular septum. The absence of the upper portion of the ventricular septum results in the lack of a zone of fixation for the atrioventricular valves, even



of septal leaflet of tricuspid valve. *d*, Incomplete cleft of anteromedial leaflet of mitral valve and of septal leaflet of tricuspid valve. *e*, Complete cleft of anteromedial leaflet of mitral valve and of septal leaflet of tricuspid valve.

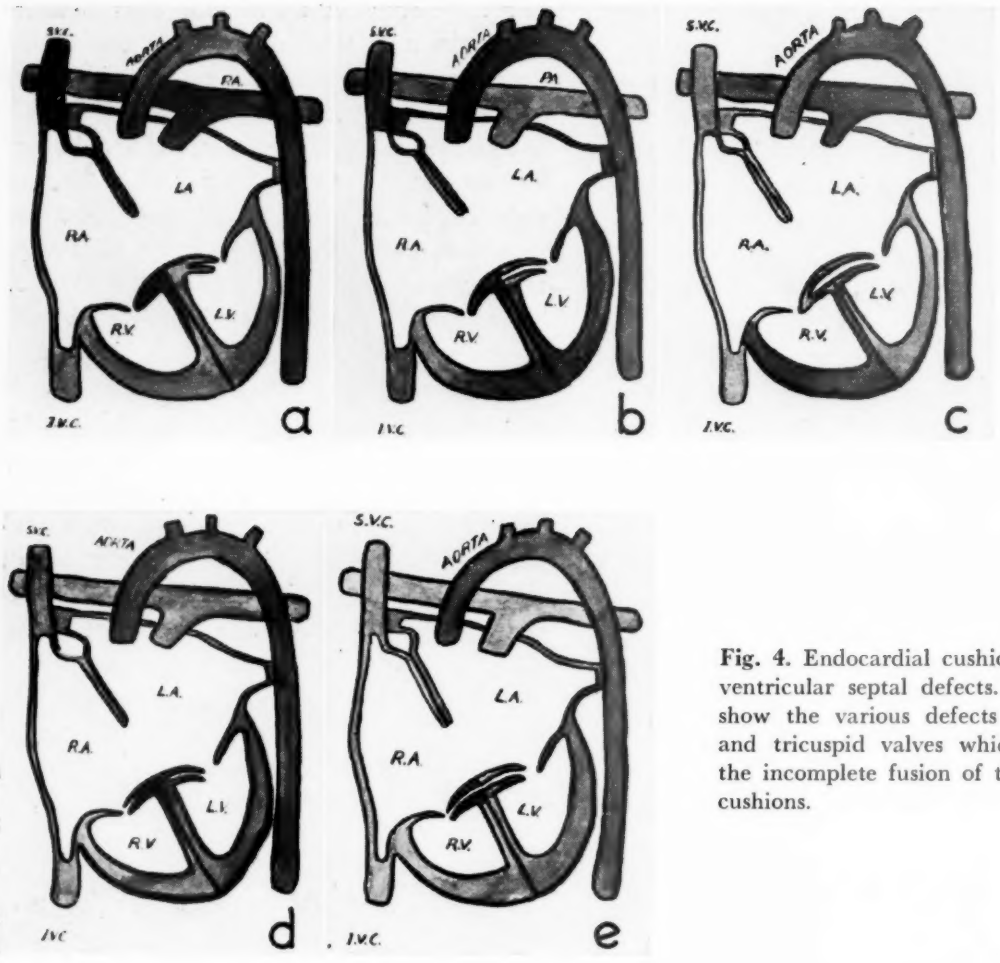


Fig. 4. Endocardial cushion defects with ventricular septal defects. The drawings show the various defects of the mitral and tricuspid valves which result from the incomplete fusion of the endocardial cushions.

when their bases are normally fused (Fig. 4), resulting in an interventricular communication.

A rare variety[8] in which the cephalad portions of the endocardial cushions developed and complete septation of the atria resulted, but a ventricular septal defect with cleft atrioventricular valves was present, also belongs to this category.

The size of the ventricular septal defect may vary from the complete absence of the septum to a defect which involves only the posterior portion of the membranous ventricular septum.

ABNORMAL RESTRAINTS OF THE ANTEROMEDIAL LEAFLET OF THE MITRAL VALVE

Studies of the normal mitral valve closure[1, 2] have shown that for practical purposes the valve orifice is guarded by 2 leaflets which constitute a flap-type valve, activated by the difference in hydrostatic pressure between the atrial and ventricular chambers and passively restrained by their anchoring chordae and papillary muscles.

The anteromedial leaflet of the mitral valve is much larger than the posterolateral one, and the chordae are attached only to the peripheral zone of the cusp. This leaves a triangular area, which is much thinner, free to billow toward the cavity of the left atrium during systole (Fig. 5). The closure of the mitral valve orifice is thus mainly effected by the freely mobile anteromedial leaflet.

In endocardial cushion defects with a cleft of the mitral valve, abnormal restraints are present. These ensure the support of the portions of the mitral valve near the cleft. Three

such abnormal restraints have been observed by us (Fig. 6). (1) There are accessory mitral chordae which anchor the valvular tissue bordering on the cleft to the ventricular septum.[2, 5, 12] It has not been sufficiently appreciated that not only do the abnormal restraints anchor the mitral valve to the ventricular septum, but also (2) there are chordae which anchor the cleft to the papillary muscles (in normal valves these chordae only run to the periphery of the cusp), and (3) a segment of the cleft, especially at the base, may be fused to the ventricular septum.

Once the cleft is closed, the restraints are no longer necessary as the normally inserted chordae will prevent eversion of the cusp. Moreover, they prevent the free mobility of the central portion of the cusp and mitral insufficiency will persist, although the cleft has been securely closed (Fig. 7).

The important point in the correction of mitral insufficiency in this anomaly is the mobilization of the leaflet by the division of the abnormal restraints.

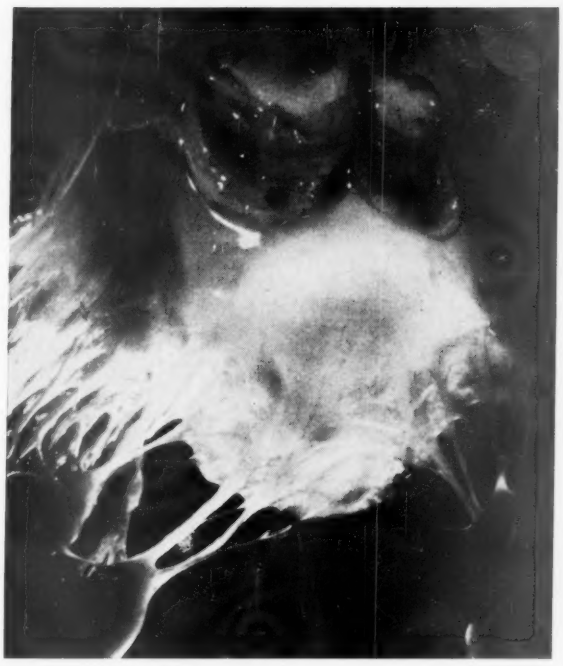


Fig. 5. A normal anteromedial leaflet of the mitral valve. Note the peripheral attachment of the chordae tendinae and the mobile central portion which is completely free of restraints.

SURGICAL REPAIR OF ENDOCARDIAL CUSHION DEFECTS

Although hypothermia with inflow stasis and the atrial well are still employed for closure of ostium secundum atrial septal defects, the only safe technique for correction of endocardial cushion defects is whole-body perfusion with or without hypothermia. We utilized the Helix reservoir bubble oxygenator system[3, 9] with high-flow normothermic perfusion for all the patients in this series.

A median sternotomy gave adequate operative exposure, although in the first 2 cases in this series a bilateral anterior thoracotomy at the level of the fourth intercostal space, with transection of the sternum, was employed.

The right common femoral or right external iliac artery was cannulated after systemic heparinization of the patient, and this cannula was secured in position and connected to the arterial line of the oxygenator.

The defect was then explored by introduction of a finger through the right atrial ap-

Fig. 6. A cleft anteromedial leaflet of the mitral valve, as seen in endocardial cushion defects, note the abnormal restraints (*a*, *b*, and *c*).

Fig. 7. A cleft mitral valve corrected by simple suture without division of the abnormal restraints (*a, b,* and *c*). This photograph clearly illustrates how the mobility of this leaflet will be impaired.

pendage. This was found to be very helpful in the evaluation of mitral and tricuspid valve function.

The inferior and superior venae cavae were catheterized through the right atrial appendage. The catheters were connected to the venous line of the oxygenator and bypass was begun. After the tapes encircling the venae cavae had been tightened around the catheters, the right atrium was opened. The incision was carried into the appendage to permit retraction of the caval catheters for optimum exposure.

A small Dever's rectractor was inserted into the right ventricular cavity through the tricuspid valve and the heart retracted anteriorly and to the left. This gave an excellent view of the valvular defects.

Cardiac asystole was not induced, as valve function could be better assessed in the beating heart. Furthermore, heart block could be detected immediately and the stitch responsible for this conduction defect could be removed at once.

The first step was a careful inspection of the various components of the anomaly. It is especially important to recognize any abnormal chordae restraining the mitral leaflet. Next, the components of the inferior margin of the atrial septal defect were studied and the presence or absence of an anatomic ventricular septal defect was established.

Endocardial cushion defects without ventricular septal defects. If abnormal restraints interfering with the free mobility of the trigone of the anteromedial leaflet of the mitral valve were present, all these were divided.[2] Immediately after this was done, the valve bulged freely with each ventricular systole. The cleft could then be repaired with interrupted No. 4-0 silk mattress sutures. If the cleft also involved the septal leaflet of the tricuspid valve, this was repaired in a similar manner.

Once the mitral valve is functioning competently, it must be kept open until the left ventricle and left atrium have filled with blood to dispel any air that may have been trapped in these chambers.

The atrial septal defect was then closed. The use of a prosthesis was always necessary. Interrupted No. 3-0 silk mattress sutures were inserted into the margin of the defect, starting at the posteroinferior margin next to the coronary sinus. The stitches should be placed superficially in this area. After each one had been inserted, the electrocardiogram was studied to make sure that there had been no interference with atrioventricular conduction. The stitches were then continued along the inferior margin of the defect, that is, along the top of the ventricular septum. If the anatomy in this area has not been carefully studied, there is a danger of including either part of the anteromedial leaflet of the mitral valve or part of the septal leaflet of the tricuspid valve in the stitches. The insertion of mattress sutures was then continued along the superior and lateral borders of the defect. Care was taken when they were placed in the torus aorticus, as in this area there is danger of piercing the anterior sinus of Valsalva with the needle. Once all the stitches were in place, each was

threaded through a compressed Ivalon or Teflon patch of suitable size. This was then slid down the stitches until securely seated on the defect before each suture was tied. When the stitches in the posteroinferior aspect of the defect are tied, development of any heart block must be detected as soon as it occurs.

The vena caval catheters were again secured in the atrial appendage and the atriotomy closed after this chamber has been allowed to fill with blood to dispel any air that may have entered.

Endocardial cushion defects with ventricular septal defects. The technical problems and dangers in the repair of this type of defect are much greater than those described in the repair of the first group.

The approach to the repair of this type of endocardial cushion defect was similar to that already described, except that after the mobilization of the mitral valve the ventricular septal defect was repaired. This repair served not only to prevent the ventricular shunt, but also to provide an area for the attachment of the bases of the anteromedial leaflet of the mitral valve and the septal leaflet of the tricuspid valve after their repair.

The closure of the ventricular septal defect must be effected in such a way as not to narrow the left ventricular outflow or damage the conducting system of the heart. This was best achieved by the use of a prosthesis sutured into position with interrupted No. 3-0 mattress sutures on the right ventricular side of the defect. A good view of the septum through the tricuspid valve orifice was possible by retraction of the heart as described. The right side of the septum was exposed and the repair begun by the careful placement of mattress sutures into the ventricular septum around the margin of the defect. Along the posterior margin the sutures must only pass through the right half of the thickness of the septum. This will minimize the danger of damaging the left bundle branch and consequently reduce the incidence of complete heart block.

Once all the sutures were in position they were passed individually through the edge of a compressed Ivalon or Teflon patch of suitable size, and the prosthesis was slid down the sutures onto the defect and tied securely in position.

Attention was then directed to the correction of the valve defect. This was done in the same way as the repair of the first type, with interrupted No. 4-0 silk mattress sutures.

The repair of this anomaly was completed by attaching the bases of the repaired leaflets to the reconstructed ventricular septum and closing the atrial septal defect with a prosthesis. This part of the repair was as described before, except that the mattress sutures along the inferior aspect were passed through the unattached basal portion of the leaflets into the newly constructed septum. When the atrial prosthesis was secured in position and these stitches were tied, the basal portions of the valves became fixed and an interventricular leak in this area was prevented.

RESULTS OF SURGICAL TREATMENT

Endocardial cushion defects without ventricular septal defects. No deaths occurred in the 10 patients in this group. One patient developed heart block, with a rapid atrioventricular nodal rhythm, which was still present 2 months after operation. The ventricular rate without treatment varied from 90 to 100 beats per minute and was usually faster than the atrial rate. The patient has returned to full activity without any disability.

Three patients in this series have reached the first anniversary after operation and their conditions have been reassessed by cardiac catheterization. All had been operated upon before the importance of the mobilization of the mitral leaflets was recognized. Mitral incompetence of hemodynamic significance was present in 2. One of these, in addition, showed a considerable interatrial shunt. This break-down of the atrial septal repair is thought to have been due to the high left atrial pressure resulting from persistent severe mitral incompetence. The

third patient had no hemodynamic evidence of mitral incompetence and no residual shunt, but the pansystolic murmur of mitral incompetence was present at the apex. Since the recognition of the importance of anomalous chordae and the appropriate treatment of this abnormality, no difficulty in correcting the mitral insufficiency has been encountered at the time of operation. However, it is too soon to report confirmation of complete correction at cardiac catheterization.

The success of the repair was assessed in the remaining patients by symptomatology, physical findings, electrocardiography, and radiology. All the patients appeared to be in excellent health with considerable subjective and objective improvement. Heart sounds and murmurs, however, were of little help in assessing the surgical result. For the most part the signs of left-to-right shunt had disappeared but the murmurs produced at the mitral valve were unchanged or even intensified. In no case in which mitral murmurs had been present preoperatively did they disappear postoperatively. The intensity of mitral murmurs bears no constant relation to the degree of incompetence.[11]

Endocardial cushion defects with ventricular septal defects. There were only 2 patients in this group. One of these died 48 hours after operation in acute pulmonary edema. The importance of dividing the abnormal restraints of the mitral valve leaflet in the successful treatment of this cardiac anomaly was clearly demonstrated by the unfortunate outcome in this case. Although the clefts in both the mitral and tricuspid valves were sutured and both the ventricular and atrial septal defects were closed, the patient was left with considerable mitral insufficiency which led to her death. Necropsy showed that the free mobility of the anteromedial leaflet of the mitral valve had been prevented by several abnormal chordae (Fig. 6).

The other patient in this group made an uneventful recovery. This case is unique in our experience in that an ostium primum type of atrial defect was present, and although the mitral and tricuspid valves were intact, there was a ventricular septal defect present and the bases of the leaflets were therefore unattached. Closure of the ventricular septal defect and fixation of the bases of the valves were necessary to stop the ventricular shunt. The postoperative course has been dramatic with complete return of the patient to normal, fully vigorous activity. Recatheterization 1 year later showed a drop in right ventricular pressure from 100/0 mm. Hg to 45/0 mm. Hg and a minute left-to-right shunt in the ventricles, only detectable by careful dye studies. No hemodynamic disturbance of the mitral valve was present though the mitral murmurs had increased in intensity.

COMMENTS

Although several reports on the treatment of endocardial cushion defects have been published, the importance of free mobilization of the mitral valve has only been reported by Edwards,[5] and surgeons have not reported cases in which this maneuver has been part of the surgical correction of the anomaly. In our experience, a better correction of the mitral insufficiency has been achieved when these abnormal restraints are recognized and divided. The only death of a patient in this series resulted from the incomplete correction of the mitral insufficiency at a stage when the importance of this aspect was not yet recognized.

The division of the abnormal chordae facilitates the closure of the cleft, permits a better view of the ventricular septum, and allows free mobility of the newly formed anteromedial leaflet of the mitral valve.

Fortunately, the most common type of endocardial cushion defect is the one without a ventricular septal defect. When the mitral insufficiency is carefully corrected, the operative mortality rate in this group should approach that of ostium secundum atrial septal defects, which in our hands has been nil.

SUMMARY

Twelve cases are reported in which open-heart surgery with the aid of extracorporeal

circulation was used for the repair of endocardial cushion defects. From the practical point of view, only 2 groups need to be recognized, those without and those with ventricular septal defects. The operative repair of the first group has been highly successful and without deaths.

The techniques for the repair of these lesions have been discussed. Of particular importance is the recognition of abnormal restraints which may prevent free mobility of the anteromedial leaflet after closure of the cleft, resulting in residual mitral incompetence. Free mobilization of this leaflet by the division of the restraints will restore the function of this cusp almost to normal.

We wish to thank Professor J. H. Louw of the Department of Surgery, University of Cape Town, for his encouraging support of our work, and the technical staff of the Marais Laboratory, Mr. C. C. Goosen, Mr. C. J. Lockett, and Mrs. V. M. Connell, for their excellent work. We are grateful to the Medical Superintendents of the Groote Schuur and the Red Cross War Memorial Children's Hospitals, Drs. J. G. Burger and J. F. W. Mostert, respectively, for permission to report details of these cases. Thanks are also due to the Council for Scientific and Industrial Research and the City Council of Cape Town, and to the Dr. C. L. Herman and Fourcade research grants for financial support.

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Polyolefin plastics as blood filters

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It is mandatory that transfused blood be passed through a filter since fibrin particles, platelet clumps, and white-cell agglutinates are found in blood even when it has been stored properly for only 3 hours.[5] These particles are capable of blocking the infusion needle and can even cause small infarcts when they enter the recipient's circulation. Deaths from multiple pulmonary emboli after transfusion of unfiltered blood have been reported.[2] Therefore, a filter is required which has a pore size smaller than the diameter of a small needle. The pores should be multiple and should lie in many directions.[4] The surface offered to filtration should contain numerous depressions so that surface debris will not tend to obstruct the filtration pores. This specification is best met by woven fibers and therefore most commercially available filters are made in such a manner. The filter should be woven of fibers which have a smooth rather than a shaggy surface. A simple tube with perforations for pores does not properly filter the blood. To be satisfactory all filters must withstand heat sterilization.

During the past 2 decades, the incidence of transfusion reactions due to incompatibility has been reduced to less than 3 per cent because of advances in immunohematology. Methods of collection and storage of blood have been improved also. Pyrogenic reactions due to contaminated transfusion equipment have been nearly eliminated. Greater attention is now being paid to the formed elements themselves. Platelets are rapidly lost from blood stored in standard glass containers. This loss can be reduced by the use of nonwettable containers, either plastic bags or siliconized glass bottles. During operations, when transfusion is likely to be massive, thrombocytopenia can lead to serious hemorrhage from all raw surfaces.[4]

In leukemic patients with thrombocytopenia, infusions of platelets promptly correct the bleeding tendencies. Patients with thrombocytopenic purpura also respond well to platelet-rich transfusions.[5, 6] Consequently, many surgeons prefer fresh blood in cases in which defects in clotting may be encountered.

Past studies have for the most part been concerned with the preservation of platelets during storage. This was considered important because of the long duration of contact between the blood and the container. Since the contact with the filter and tubing system is brief, these factors have not been scrutinized with the same thoroughness. Our investigation was devised to ascertain the extent of platelet loss that occurs during passage of whole blood through commercially available blood filters. We have also investigated new filter constructions which embody the features we consider desirable.

METHODS AND MATERIALS

In a group of patients with secondary polycythemia, the blood was typed by the

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standard method. Three patients with type A blood were used as donors. Five hundred milliliters of blood was collected in plastic containers from each patient. Samples from each patient were cross-matched and found to be compatible. The 3 units were combined in a large nonwettable container and experiments were performed within an hour after collection. Platelet counts were made by the Dameshek method on the mixed samples.[7] Four commercially available filters were obtained and 300 ml. of blood was run through each. Five platelet counts were made on the final 10 ml. of the sample run through each filter. In addition to the commercially available filters, we tested polyolefin plastic filters which had been constructed by braiding or weaving the fibers into tubes. Polyolefin and halogenated polyolefin plastics include polyethylene, polypropylene, polytetrafluoroethylene, and others. Of these, linear high-density polyethylene and polypropylene are

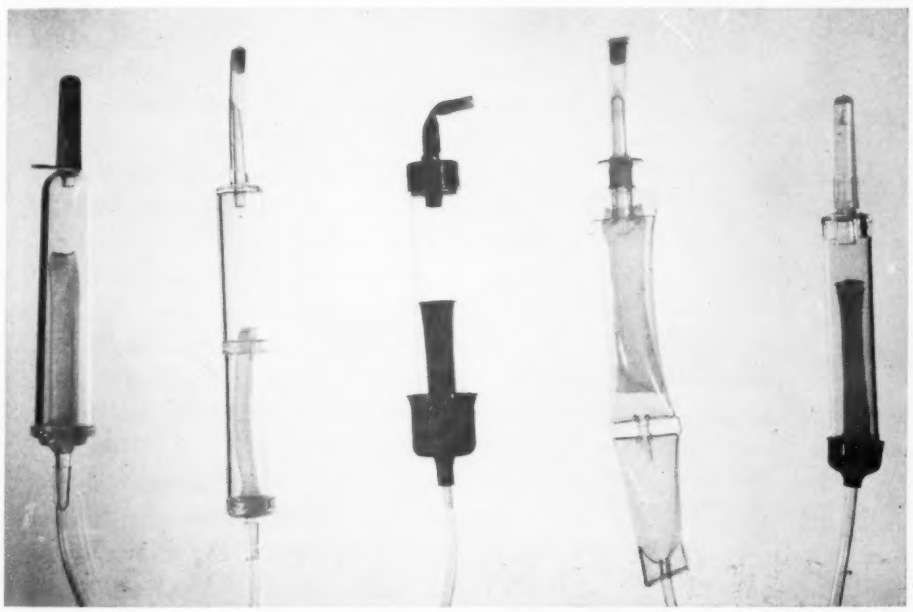

Fig. 1. The filters tested. The filter on extreme right is the new type.

Fig. 2. All filters tested show adsorption of dye, except the linear polyethylene filter on the right.

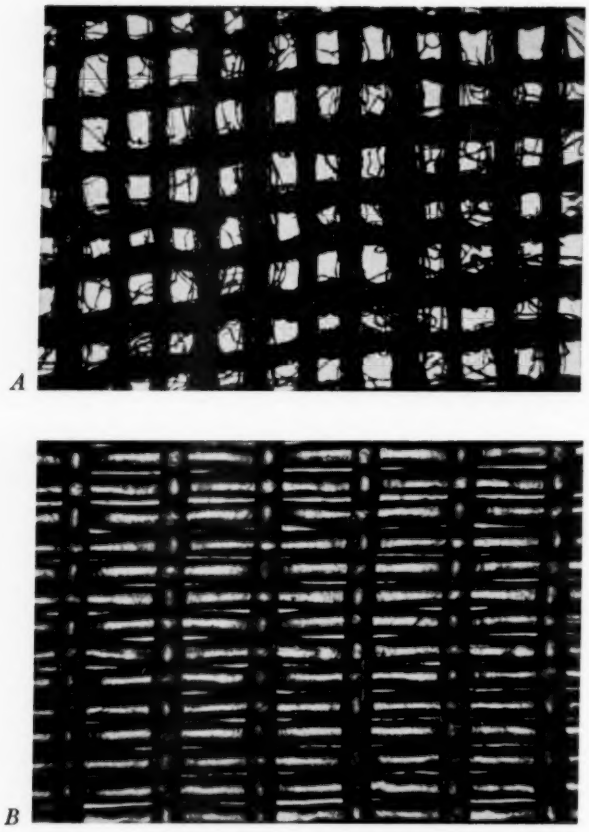

Fig. 3. *A,* The bakelite-impregnated cotton filter shows many irregular branches which partially occlude filter pores. *B,* Polyethylene fibers are monofilaments and entirely free from branches.

inexpensive, resistant to steam sterilization, and can be easily heat sealed. Polypropylene can be autoclaved but polyethylene can only be boiled. The types of filters are shown in Fig. 1. Upon completion of the experiments, the filters were removed from the drip bulb and rinsed with distilled water to remove all nonadherent blood and protein. They were then immersed for 3 minutes in a cresyl violet stain used to stain platelets in platelet counts, and again rinsed with distilled water.

RESULTS

The platelet counts after the passage of 300 ml. of fresh blood through the various filters are presented in Table I. Filters Nos. 1 through 4 are commercially available. Filter No. 5 is the polyolefin filter. Variations in platelet count between the types of commercial filters tested are not significant. The platelet concentration in all cases was decreased by approximately 40 per cent after a single passage of 300 ml. of blood through the filter. If a filter is used for more than this amount of blood, a greater percentage of platelets probably would be removed. As platelets are removed, the interstices of the filtering surface are blocked by the platelet clumps. The resistance offered to filtration is so increased that the rate of flow through commercially available filters is reduced. With the nonwettable polyolefin plastic filters used by us, there was no reduction in platelet count after filtration of 300 ml. of blood. Since the rate of filtration remains almost constant, no blocking of the interstices occurs. This type of filter may therefore be used for many units of blood.

The absorption of dye in the various filters is shown in Fig. 2. The electrostatic configuration of this dye is such that it is attracted of platelets and bound to them by ionic charge. This is the same mechanism by which the platelets are absorbed onto the filters. Only in a nonpolar and therefore nonwettable filter is there lack of adsorption of the brilliant cresyl blue.

Photomicrographs show a comparison between the newly designed filter with smooth fibers to one commercially available filter (No. 3) which has a shaggy appearance (Fig. 3). It is important that blood be passed over smooth surfaces only. Allen[1] has shown a reduction in platelets of 53 per cent in blood passed over a rough surface.

SUMMARY AND CONCLUSIONS

The filters supplied with the commercially available transfusion sets cause an extensive

Table I. *Platelet counts after passage of 300 ml. of fresh blood*

	Platelet count	*% reduction from control*
Control	365,000	0
Filter No. 1	228,000	38
Filter No. 2	215,000	42
Filter No. 3	233,000	37
Filter No. 4	241,000	34
Filter No. 5	362,000	2

reduction in platelet concentration during one passage. A newly designed plastic filter is described which obviates this difficulty and still offers adequate filtration for transfused blood. The choice of a filter which will not reduce the number of platelets is of great importance in massive transfusions, in hemorrhagic disorders, and especially with extracorporeal circulation.

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Polarographic evaluation of the effect of Pitressin on hepatic oxygen tension

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The liver has both portal venous and hepatic arterial blood available for fulfillment of its cellular oxygen demands. In the normal animal, the portal vein supplies 75 per cent of hepatic blood.[12] However, because of the relatively lower oxygen saturation of portal blood, the hepatic arterial supply is the major source of oxygen for the cells.[2] Previous investigators[3, 4, 10] have shown that Pitressin lowers portal flow, pressure, and portal venous oxygen content. The associated effects on the hepatic artery and, more particularly, on liver oxygen tension have not been studied.

Under controlled experimental conditions, changes in hepatic tissue oxygen tension have been used to reflect changes in both arterial and portal circulation. By means of the polarographic recording of changes in the hepatic tissue oxygen tension during occlusion of the vascular supply to the liver and during the intravenous administration of Pitressin, the physiologic aspects of hepatic circulation and the pharmacologic aspects of Pitressin have been investigated. The experiments indicate that, in normal animals, the hepatic arterial and portal venous flows are reciprocal and a temporary decrease in portal venous flow is accompanied by a simultaneous increase in hepatic arterial flow. Pitressin has been demonstrated to be a generalized vasoconstrictor which affects the hepatic arterial circulation but acts on the splanchnic arterioles to a greater extent.

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METHODS

Measurements of hepatic tissue oxygen tension were performed by the same technique in all experiments.[5, 12] The ends of the cathode and anode were inserted into the liver parenchyma with minimal trauma. The leads from the electrodes were then connected to a modified polarograph and a constant voltage of –0.65 v. was applied to the platinum cathode. Changes in oxygen tension were recorded in millivolts and converted by the application of Ohm's law to microamperes. The results were expressed as delta microamperes relative to an established base line.

Mongrel dogs which weighed 20 to 24 kilograms were anesthetized with intravenous pentobarbital sodium. Ventilation with 100 per cent oxygen by means of a positive pressure respirator was employed. A thoracoabdominal incision was made through the right tenth intercostal space and the portal vein and hepatic artery were then exposed and mobilized at the porta hepatis. After the electrodes had been inserted into the liver, the brachial artery was cannulated and the arterial blood pressures monitored with a mercury manometer. Base line recordings of the oxygen tension were then established. Changes in oxygen tension were continuously recorded during occlusion of either the hepatic artery, portal vein, or both vessels.

The effects of Pitressin (Parke, Davis & Company) on hepatic tissue oxygen tension in control animals and in those with occluded hepatic arteries or end-to-side portacaval shunts were measured. In the

group with portacaval shunts, an end-to-side anastomosis was performed 2 weeks prior to the investigative procedure. Pitressin was administered into the femoral vein as a solution of 5 U. in 80 ml. of dextrose in water over a 4 to 6 minute period. A minimum of 4 preparations was used for each factor studied.

RESULTS

Changes in the amount of oxygen available to the liver parenchyma accompanying occlusion of the hepatic artery, portal vein, and both vessels in control animals are shown in Fig. 1. The changes associated with hepatic artery occlusion in animals with previous end-to-side portacaval shunts are also demonstrated. Hepatic artery occlusion in the control group caused an immediate decrease in the amount of oxygen available to the liver cells (Fig. 2), with no change in arterial pressure. When the portal vein was occluded (Fig. 3), there was an increase in oxygen tension for a period of 4 to 5 minutes followed by a fall to levels below the original base line. This fall in oxygen tension was associated with a simultaneous decrease in systemic arterial pressure. When the hepatic artery and portal vein were occluded simultaneously, the decrease in liver oxygen tension was greater than that which resulted from occlusion of the hepatic artery alone. The most marked decrease in the hepatic oxygen tension in all preparations studied followed hepatic artery occlusion in dogs with previously established portacaval shunts (Fig. 4).

The changes in hepatic oxygen tension associated with the administration of Pitressin are demonstrated in Fig. 5. In the control group (Fig. 6), there was an immediate and sustained elevation in oxygen tension which lasted 20 to 40 minutes and then decreased to the original base line. Concomitant elevations in systemic arterial pressure were inconsistent and, if present, were only transient and minimal.

In the group of dogs in which hepatic arterial ligation had been carried out just prior to the administration of Pitressin, the drug had relatively little effect on the post-occlusion base line.

In the animals which had undergone end-to-side portacaval anastomosis 2 weeks prior to investigation, Pitressin caused a marked and sustained decrease in the amount of oxygen available to the liver cells. This decrease lasted 20 to 30 minutes with a gradual return to normal base line readings.

The acute experiments were all carried out over a 1-hour period and during this time there was no evidence of platinum electrode poisoning or decay.

DISCUSSION

Stationary platinum electrode polarography provides a practical technique for the determination of the amount of oxygen available to tissue.[9, 12] Absolute measurements of tissue oxygen tension by this technique are presently not feasible. However, in the acute experimental situation in which the oxygen tension of the arterial blood remains constant and when there is no

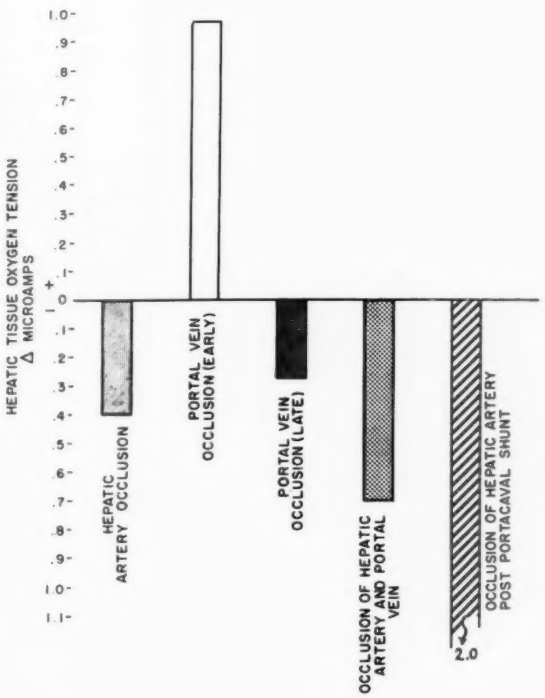

Fig. 1. Effect of occlusion of hepatic artery and portal vein on hepatic tissue oxygen tension. Bar represents average of 4 preparations studied.

significant alteration in tissue metabolism, relative changes in tissue oxygen tension reflect relative changes in blood flow to the area.

The decrease in liver oxygen tension after occlusion of the hepatic artery in control animals, although consistent, is not marked. However, with an established portacaval shunt and a liver therefore totally dependent on hepatic arterial flow for its nutrient supply, occlusion of the artery causes a precipitous reduction in hepatic oxygen tension. The finding of an initial increase in liver oxygen tension associated with occlusion of the portal vein indicates a reciprocal increase in arterial flow to the liver. This supports the theory, proposed by Herrick,[6] that portal venous and hepatic arterial flows to the liver terminate in a common inflow channel. The eventual decrease in liver

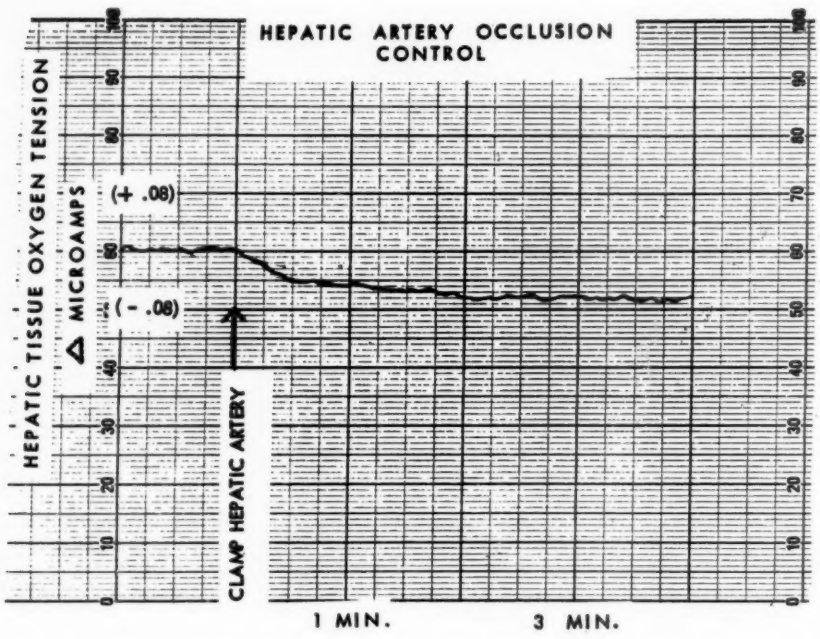

Fig. 2. Hepatic artery occlusion control. Direct tracing reproduction.

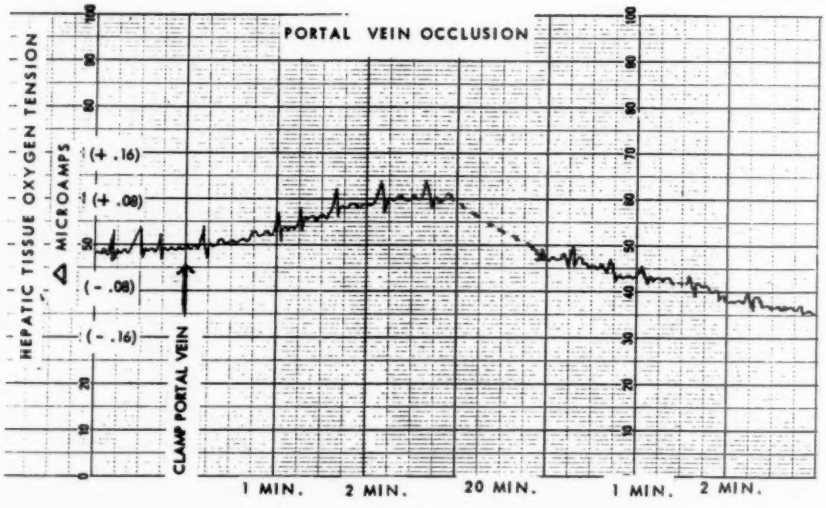

Fig. 3. Portal vein occlusion. Direct tracing reproduction.

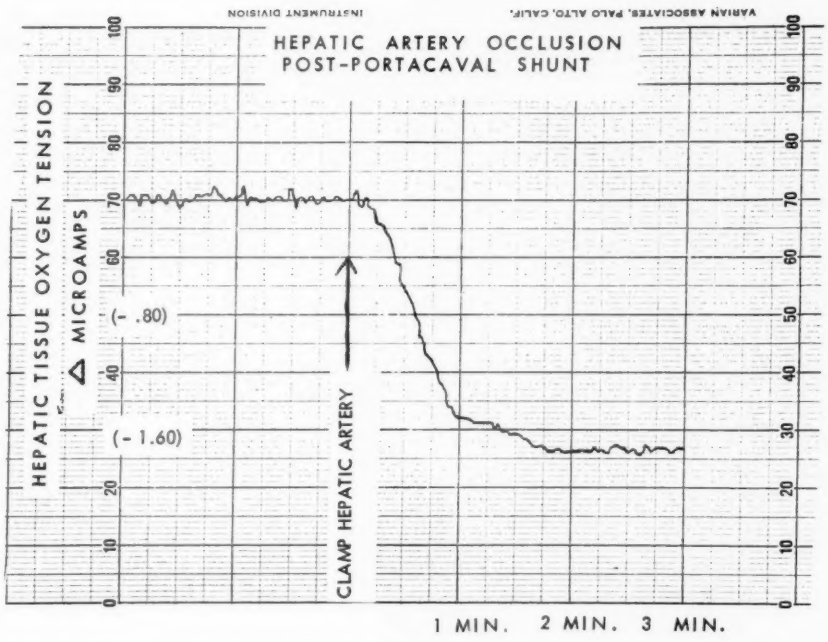

Fig. 4. Hepatic artery occlusion after portacaval shunt. Direct tracing reproduction.

oxygen tension in the animals is explained by a marked decrease in arterial pressure which has been demonstrated to occur with prolonged portal vein occlusion.[13]

Davis and associates[3] have shown that Pitressin has little effect on arterial pressure, cardiac output, and hepatic metabolism. A major action of the drug results in the redistribution of blood flow with diversion of flow from the splanchnic bed. This diversion has been considered to be caused by constriction of splanchnic arterioles[7, 8] or by alteration of flow through the gastroenteric arteriovenous shunts.[1, 4] The end result is a decrease in portal pressure, flow, and portal venous oxygen saturation.[3, 5, 10] As is the case with a mechanical decrease of portal venous inflow to the liver, the intravenous administration of Pitressin produces an increase in the amount of oxygen available to the liver cell. The fact that the administration of the drug to animals with portacaval shunts causes a decrease in the amount of oxygen demonstrates that Pitressin is a generalized vasoconstrictor affecting the hepatic arterioles. In the control animals, the action is not apparent since the effect

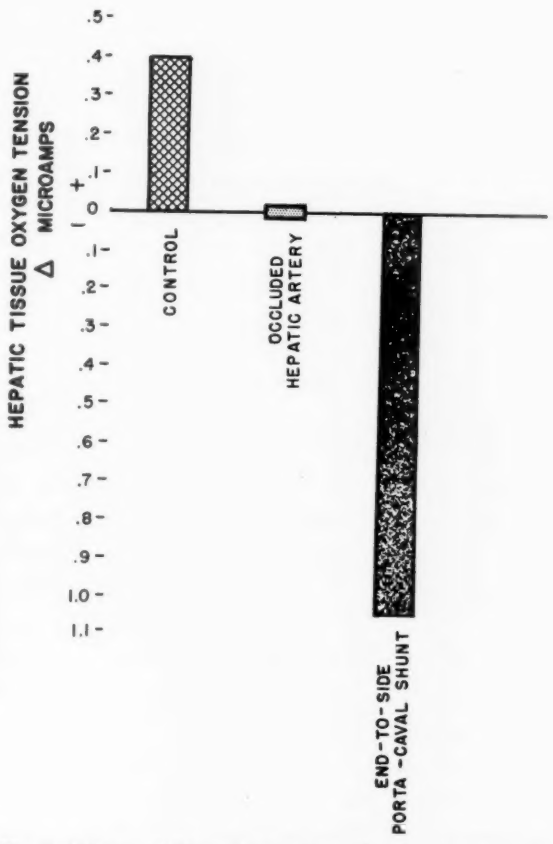

Fig. 5. Effect of Pitressin on hepatic tissue oxygen tension. Bar represents average of 4 preparations studied.

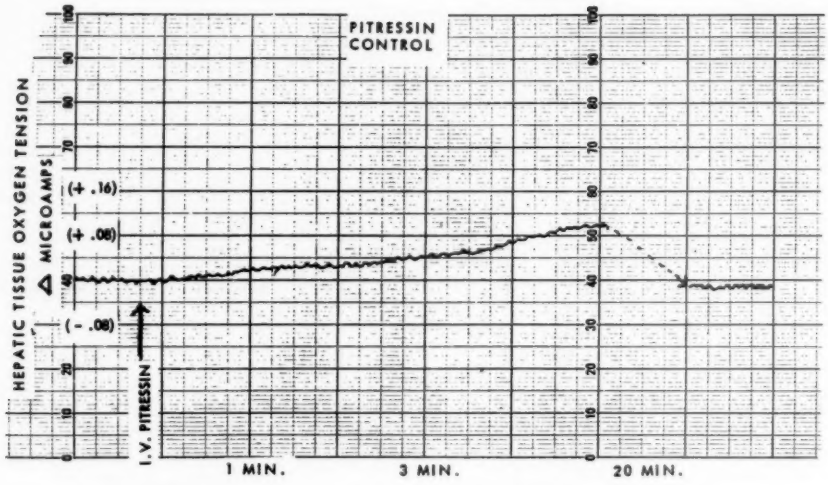

Fig. 6. Pitressin control. Direct tracing reproduction.

on splanchnic arterioles is more marked and a relative increase in hepatic arterial flow to the liver occurs.

Pitressin and surgical Pituitrin have been used effectively as means of reducing portal hypertension and controlling the bleeding from esophageal varices.[10] In the cirrhotic patient with portal hypertension, in whom the portal vein carries blood to the liver, the administration of the drug should, according to our experimental findings, increase the amount of oxygen available to the liver cell. However, in the situations in which the portal vein serves as a hepatofugal conduit or when portal hypertension follows portal vein thrombosis or thrombosis of a portacaval shunt, reduction in hepatic oxygen tension may take place and thus theoretically may cause significant liver anoxia. Studies of the effects of Pitressin on hepatic oxygen tension of cirrhotic patients during operations, both before and after portacaval shunts, are proposed to resolve this problem.

SUMMARY

Stationary platinum electrode polarography provides a means of evaluating the effects of vascular occlusion and Pitressin on hepatic tissue oxygen tension. An acute decrease in portal flow results in a reciprocal increase in arterial flow. Pitressin is a generalized vasoconstrictor acting preferentially on the splanchnic bed, but also having a direct effect on the hepatic arterial circulation. The application of these experimental findings to clinical situations is discussed.

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Temporary superior mesenteric–femoral vein bypass to obtain survival in dogs during occlusion of the portal vein

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The current clinical management of major bleeding as a complication of portal hypertension usually includes portal decompression by the surgical construction of a shunt between the portal and systemic venous circulations. Adequate evaluation of the standard extrahepatic anastomoses and of intrahepatic shunts under study has been hindered by the high mortality rate in dogs after occlusion of the portal vein for a period long enough to create the experimental preparation. A technique has been developed in the laboratory which regularly permits survival in dogs after portal vein occlusion lasting for up to 90 minutes.

EXPERIMENTAL METHOD

Mongrel dogs were anesthetized by either ether inhalation or a veterinary solution of pentobarbital sodium administered intravenously. A right paramedian oblique incision was made. The portal vein was exposed and dissected caudad beyond the junction of the splenic vein and cephalad to its bifurcation at the liver. An incision was made in each groin, with exposure and cannulation of the left femoral vein for fluid and blood replacement, the right femoral vein for the superior mesenteric–femoral bypass and the right femoral artery for blood pressure estimations. The dogs were heparinized (1.5 mg. per kilogram). The splenic artery was ligated and the superior mesenteric vein intubated with a No. 14 Bardex plastic catheter by way of the splenic vein. The portal blood was diverted through Mayon plastic tubing, $\frac{3}{16}$ inch in diameter, through the Sigmamotor pump into the right femoral vein at the rate of 15 ml. per kilogram per minute (Fig. 1). (A normal portal blood flow is 30.1 ml. per kilogram per minute. More vigorous pumping caused collapse of the tube and congestion of the portal bed.)

The portal vein was clamped and, if a portocaval shunt was planned, the gastroduodenal branch was ligated and divided and the portal vein ligated and divided close to its bifurcation. The end-to-side portocaval shunt was established by the usual suture technique. The catheter was withdrawn from the splenic vein and splenectomy performed. Protamine sulfate was given (3 mg. per kilogram), all the cannulas withdrawn, and the wounds closed.

RESULTS

The results have been divided into 2 groups. In the first, the portal vein was clamped initially without preliminary diversion of its flow. All 6 dogs died and at autopsy intestinal infarction and intra-

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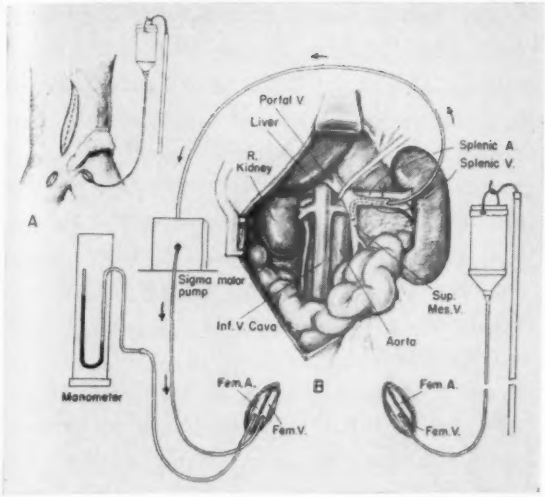

Fig. 1. Diagram of superior mesenteric–femoral vein bypass.

luminal hemorrhage were found. An unsuccessful attempt was then made to divert the portal blood by direct intubation of the portal and superior mesenteric veins. Four animals maintained an adequate blood pressure during occlusion of the portal vein, but died after extubation from hemorrhage and obstruction of the portal vein, which had been sutured in haste without clamping. Two died of hemorrhagic shock during these manipulations.

In the second group (14 dogs), the superior mesenteric vein was intubated via the splenic vein. The dogs tolerated the procedure well. There was no congestion of the portal circulation and no shock. The arterial blood pressure was stable. Some transient fluctuations were due to manipulation, the blood loss into the tubing (80 to 100 ml.), and bleeding and oozing resulting from heparinization. The blood loss was replaced. One of the dogs died on the operating table in consequence of a technical error in intubation of the superior mesenteric vein and inadequate function of the pump.

One dog died 12 hours after the procedure, and 450 ml. of unclotted blood was found on autopsy in the abdominal cavity. The portocaval anastomosis was patent and no thrombosis of the portal vein was found. One dog died 11 days postoperatively of intercurrent infection. At autopsy the portal system was found to be patent. Ten of the remaining 11 dogs were sacrificed from 1 to 44 days after the operation, and a second exploratory operation was performed on one on the forty-first postoperative day. In each instance the portal system was patent and there were no signs of infarction or hemorrhage. The dogs had received 600,000 U. of penicillin 1 day before and 3 days after the procedure.

Fig. 2 demonstrates the observation that no fall in blood pressure followed clamping of the portal vein. In contrast, Fig. 3 illustrates the arterial blood pressure in an example of fatal cross-clamping of the portal vein without a bypass.

DISCUSSION

Acute total occlusion of the portal vein in dogs is accompanied by a very high mortality rate. Ore,[18] Schiff,[23] Bernard,[1, 2] Eck,[9] and Solowieff[24] in the nineteenth century and Neuhof,[17] Elman and Cole,[10] Boyce,[3] Brunschwig,[4] Schafer and Kozy,[22] and Markowitz[16] in the twentieth century, concluded that dogs, cats, and rabbits all die more or less promptly after sudden and complete occlusion of the portal vein. The cause of death is attributed to shock due to sudden exclusion of a volume of blood from the general circulation. Johnstone[14] suspected some unknown etiologic factor and Boyce[3] implicated a neurogenic factor.

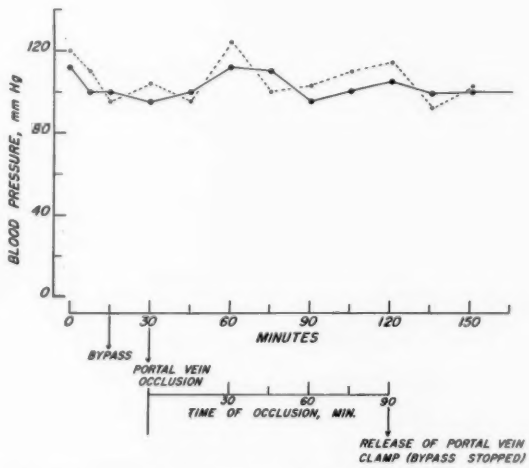

Fig. 2. Recording of arterial blood pressure in dogs with occlusion of portal vein and bypass.

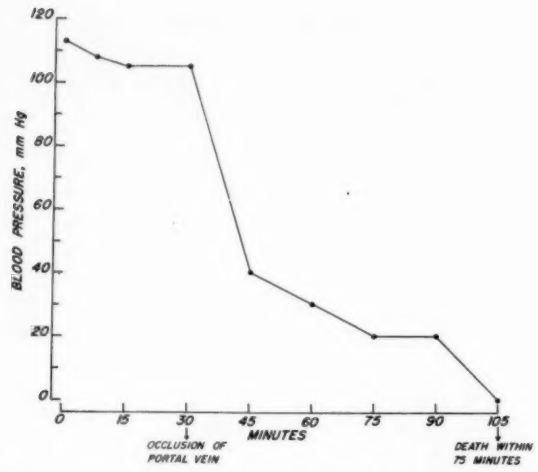

Fig. 3. Recording of arterial blood pressure in a dog with occlusion of the portal vein without bypass.

According to Heimburger and associates,[11] the portal blood flow in lightly anesthesized dogs is stable for 1 hour, with some individual variation. The average flow obtained was 30.1 ml. per kilogram per minute and corresponds to 23 per cent of the total cardiac output. Thirty minutes after occlusion of the portal vein the circulating blood volume is reduced to 40 to 42.1 per cent.[11, 14] Consequently the blood pressure drops after 10 to 20 minutes to a level of 30 to 40 mm. Hg and declines slowly until death. The survival time in dogs is given variously by Elman and Cole[10] as 66 minutes, by Johnstone[14] as 79.7, and by Tanturi and colleagues[25] as 125. Surprisingly, the dogs of the latter group survived after 45 minutes of portal vein occlusion, with electrocardiographic changes characteristic of myocardial infarction.

Many attempts have been made to prevent death of the animals. It may be avoided by construction of a preliminary portocaval shunt (Eck's fistula[9]), or by occlusion of the portal vein in stages, permitting the blood to escape through collateral circulation. Ore[18] in 1856 was the first to demonstrate the feasibility of gradual occlusion of the portal vein in dogs. The abdomen was opened (without asepsis), the portal vein isolated, and a thread passed beneath it. After the abdomen was closed the 2 ends of the thread were tied over the animal's back. On the fourth day the thread was pulled out. The inflammatory reaction and pressure gradually induced thrombosis. Two dogs survived. Brunschwig[4] modified the experiment, with the ligature gradually severing the thrombosed vein. Solowieff[24] showed that dogs may be saved by ligation of the branches of the portal vein in stages, and Neuhof[17] obtained survival by progressively constricting the lumen of the portal vein in several operations.[12] Elman and Cole[10] could postpone but not prevent death by massive blood transfusions and clamping of the aorta above the celiac axis. Hoffman and Freedlander[12] prevented death of the animals by preliminary transposition of the spleen into the chest, thus creating collateral circulation.

Schafer and Kozy[22] succeeded in performing an end-to-side portocaval shunt by using a rapid nonsuture technique (Blakemore tube) and massive blood transfusions. Daniel,[7] who performed grafting of an excised segment of the portal vein, reported survival if the portal vein was occluded for less than 14 minutes. Child[5, 6] demonstrated that the *Macaca mulatta* monkey and human beings can tolerate sudden occlusion of the portal vein. He failed, however, to perform a one-stage pancreatoduodenectomy with resection of the portal vein. Five of 6 monkeys died of uncontrolled hemorrhage caused by congestion of the portal system. He succeeded in performing a two-stage operation in monkeys and in human beings, the first stage of which was ligation of the portal vein. In 1 human subject the lumen of the portal vein was not invaded. Child recommended a one-stage operation if the lumen of the portal vein is involved, and otherwise a two-stage procedure.

Brunschwig[4] reported a one-stage pancreatoduodenectomy with resection of the portal vein in a patient with multiple adhesions from a previous operation. The collateral circulation was thought to be responsible for the survival. Parsons[19] and Person and Devine[21] arrived at the same conclusion. In 2 cases of ligation of the portal and splenic

veins after trauma, Patton and Johnston[20] reported the subsequent development of portal hypertension which necessitated secondary shunting of coronary and superior mesenteric veins to the vena cava. Dermott[8] and Hubbard[13] performed end-to-side superior mesenteric–caval shunts after pancreatoduodenectomy and resection of the portal vein. The patients survived the operation, but 1 of Dermott's and 2 of Hubbard's died of ammonia intoxication and fatty infiltration of the liver. These cases demonstrate that human beings tolerate a portocaval shunt poorly in the absence of portal hypertension, and direct anastomosis or grafting of the vein segment has been recommended. Daniel[7] attempted to bridge defects of the portal vein in dogs, but 14 minutes of clamping was crucial for survival. Kikuchi[15] restored the continuity of the portal vein of a human subject after pancreatoduodenectomy by a homologous alcohol-preserved vein graft, which was patent at autopsy 27 days after operation.

From the review of the literature it may be concluded that, while acute occlusion of the portal vein in dogs is almost uniformly lethal, in human beings it may be compatible with survival, with the risks of shock, uncontrollable hemorrhage (during resection of the pancreas in a congested field), intestinal infarction, and ultimate portal hypertension. Replacement of the excised segment of portal vein during pancreatoduodenectomy may ultimately be of value.

Attempts were made to find a method which would permit clamping of the portal vein for a sufficient length of time to complete reconstructive procedures of the divided portal vein without the risk of congestion of the portal bed and subsequent shock and death. This was accomplished by diversion of the portal blood temporarily to the systemic circulation by means of a superior mesenteric–femoral vein bypass. With this maneuver the portal vein could be clamped at its bifurcation in the hilus of the liver for 90 minutes and, if necessary, divided and anastomosed end-to-side to the inferior vena cava. The dogs tolerated intravenously administered Nembutal anesthesia which, according to Child[5] and Schafer and Kozy,[22] is contraindicated in cases of portal vein obstruction.

SUMMARY AND CONCLUSIONS

1. Dogs do not tolerate acute occlusion of the portal vein, presumably because of the hypovolemic shock secondary to the trapped blood in the portal circulation.

2. A temporary superior mesenteric–femoral vein bypass regularly permits occlusion of the portal vein in dogs for at least 90 minutes, with survival.

3. This technique will permit a variety of reconstructive and shunting procedures involving the portal system in dogs without limitation of the time of occlusion.

4. The temporary superior mesenteric–femoral vein bypass may be useful in human beings for decompression of the portal bed during dissection of the pancreas and reconstruction or diversion of the portal vein.

The assistance of surgical technicians Ruthven Ferreira, Ivan Henry, and Kendrick McCord was invaluable in these experiments.

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Failure of separation of larynx and trachea from the esophagus: persistent esophagotrachea

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Esophageal atresia with a fistula from the lower segment of the esophagus to the trachea is a relatively common and well-recognized deformity. Since Thomas Gibson,[1] in his book *The Anatomy of Human Bodies Epitomised,* described this condition clearly in 1696, several hundred cases have been described in the medical literature.[3] Plass,[11] in a review article 30 years ago, cited 204 references. Ladd[6] subdivided the types of deformity into 5 groups, of which by far the commonest is type 3. The complete failure in the development of a septum dividing the primitive esophagotrachea into trachea and esophagus, leaving instead a common tube of the larynx and the whole main length of the trachea and esophagus, is so rare that it does not come into his classification. Richter,[12] in a thesis for the degree of Doctor of Medicine in Leipzig in 1792, described this condition in the words "digitoque admoto gula cum larynge in communem saccum videretur" ("putting my finger there the gullet and larynx were seen to be joined together in a common cavity").

Two cases in siblings and a third isolated case are reported here.

CASE REPORTS

Case 1. A boy weighing 4 pounds, 2 ounces, was born after 35 weeks gestation. The mother had shown hydramnios. When the first attempt at feeding was made 36 hours after birth, he became cyanosed, and this recurred at every further attempt at sucking. When a catheter was passed the child became cyanosed but the tube passed easily into the stomach. Lipiodol passed directly into the stomach but it also appeared in the bronchial tree. On admission to the hospital the infant's general condition was extremely poor and it was only possible to carry out a gastrostomy. The child died a few hours after admission at the age of 4 days. At necropsy the only gross abnormality found was in the respiratory tract. The nose, hard and soft palate, uvula, and epiglottis appeared normal. The back of the larynx was open and allowed free and direct communication between the cavity of the larynx and that of the upper esophagus. The tracheoesophageal septum was completely absent for 4 cm. (Fig. 1). Immediately above the bifurcation of the trachea, the posterior wall of the trachea was represented by a thin membrane. The lung showed normal lobulation. The esophagus had a pouch approximately 1 cm. deep which arose below, just above, and immediately behind the bifurcation of the trachea and terminated just below the origin of a tracheogastric fistula. The rest of the intestinal tract showed no abnormality.

Case 2. Two years after the death of the child in Case 1, the mother had a normal pregnancy and gave birth to a normal child.

Two years later a third pregnancy occurred and was again complicated by hydramnios. The baby regurgitated a large amount of mucus immediately after birth. When 3 days old it became extremely cyanosed while feeding and a tracheoesophageal fistula was suspected. A catheter passed freely to the stomach. A roentgenogram taken with the tube in position showed that the tube passed to the stomach, but there was one curious feature in the lateral picture. The tube seemed to be a long way forward—well in front of the spine (Fig. 2).

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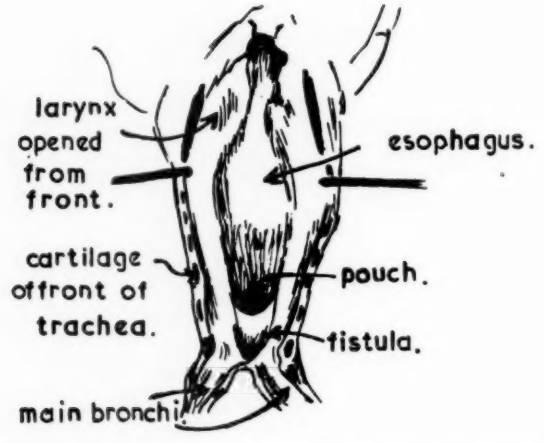

B

Fig. 1. The esophagotrachea from Case 1 in which the larynx, trachea, and main bronchi have been opened longitudinally from the front. *A,* The necropsy specimen. *B,* Diagrammatic sketch of the anomaly.

On the passing of a bronchoscope the 2 main bronchi were visible at the lower end, but as the bronchoscope was withdrawn it was seen to slip between the cartilages of the larynx and could be moved backward and forward without difficulty.

An attempt was made to perform a plastic repair in 2 stages. First the larynx and upper trachea were approached by a transverse incision in the lower part of the neck and a septum was formed by direct suture of the lateral walls of the combined esophagotracheal tube. On the following day the right side of the chest was opened and the esophagus separated from the trachea from below upward. The baby did not survive, however, for more than 24 hours.

Necropsy showed that a complete common tube had been present from the larynx to the bifurcation of the trachea. There was no blind-end pouch and fistula as in the previous child, but the esophagus continued directly at the bifurcation of the trachea. No other gross abnormalities were found in this child.

Two years after the child's death a fourth child which was normal was born to the parents.

Case 3.* A female child was born weighing 3 pounds, 10½ ounces, and was obviously immature. The mother had shown hydramnios. At birth the child was described as "mucousy" and was occasionally cyanosed. She was admitted to hospital when 4 days old. An opaque tube passed into the stomach without difficulty. The esophagoscopy findings were identical to those described in Case 2. There was no separation of the esophagus and trachea, and lack of fusion of the posterior larynx. The condition was not thought to be amenable to surgical treatment. Necropsy confirmed the clinical findings but also showed a small diverticulum of the unfused larynx which arose on the left side below the thyroid cartilage. No other gross abnormalities were found in this child.

MORBID ANATOMY

All 3 children died with aspirated material in the lungs. The inflammatory reaction in Case 1 was of slightly longer standing than in the other cases. In all children the epiglottis appeared normal, as did the false and true vocal cords, and the anterior parts of the thyroid and thyroid cartilages. Except for the failure of fusion of the larynx at the posterior end, the cartilage structure of the larynx appeared normal but splayed. The tracheal cartilages appeared

*This case was seen by Miss Forshall, Mr. Rickham, and Dr. Hall of Liverpool and we are describing their findings.

spread out to form approximately a semicircle. The general structure in Case 2 was considerably modified by the operation. Serial blocks were taken over the whole length of the specimens (Fig. 3, *A* and *B*). Both longitudinal and transverse muscle bundles were present in the esophagus. The squamous esophageal epithelium, however, was not confined to the posterior wall of the common tube, but extended a considerable way around the side and within the orbit of the tracheal cartilages, and the posterior walls of the operatively reconstructed trachea contained much esophageal mucosa.

DISCUSSION

The incidence of this particular deformity is difficult to assess. Such lesions would normally be registered as congenital tracheoesophageal fistulas. Haight[3] found that simple tracheoesophageal fistula, without atresia, constitutes approximately 3 per cent of deformities of the esophagus. In his series of 500 case reviews, only one patient seemed to have had an associated involvement of the larynx and that child also had agenesis of the lungs.[7] Petterson[10] described a case in 1955. Ingalls and Prindle[5] described no such case in their series of 107 cases of atresia and fistula. Tracheoesophageal fistula in siblings is also rare. Ingalls and Prindle,[5] who went through the family histories of their patients in great detail, saw no evidence of a genetic determination in this condition. "None of the families of the 107 infants in this series is known to include another member with esophageal atresia or fistula either in the same or preceeding generations." The only reference to other cases in siblings appears to be that of Lanman[8] who described a boy with the usual type 3 atresia and fistula with anal atresia, who was followed a year later by a sibling with atresia and fistula but no anal lesion.

In the present cases the clinical histories were similar, with "mucousy" mature babies born to mothers who had pregnancies with hydramnios. Previous to esophagoscopy, the observation in Case 2 of the extreme anterior position of the opaque catheter in the lateral roentgenogram probably constitutes a useful guide to diagnosis (Fig. 2).

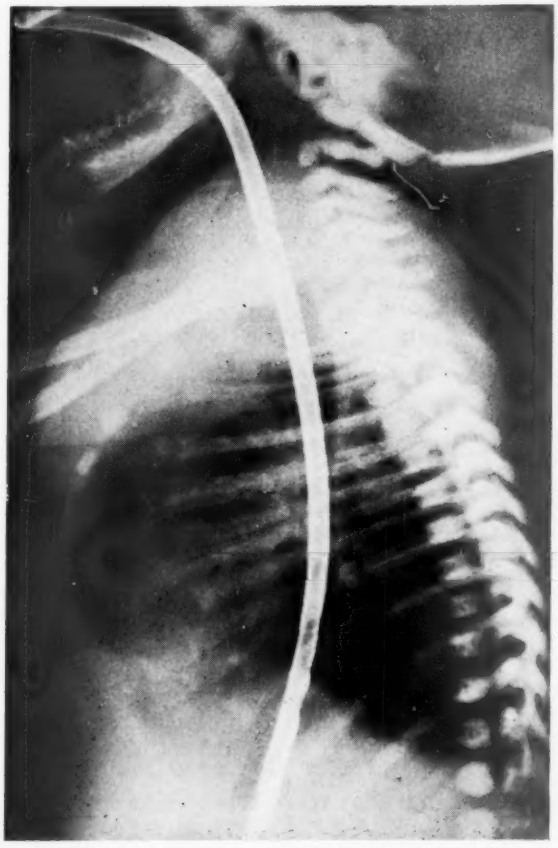

Fig. 2. Reproduction of roentgenogram of the opaque catheter lying in the esophagotrachea in Case 2.

Attempts at operative repair in these cases are bound to be less successful than in instances of the usual atresia and fistula.

The only successful treatment of this type of deformity that we have found is reported by Petterson.[10] In his patient, however, the deformity involved only the larynx and the upper 2 or 3 rings of the trachea. The lowest part of the defect was at the lower margin of the thyroid gland. At operation the esophagus was separated from the larynx and trachea and each uniform channel was closed. A tracheotomy was performed immediately after operation and was not closed for 6 months, but the child made a good recovery.

In the more extensive type of lesion such as we have described, it would seem desira-

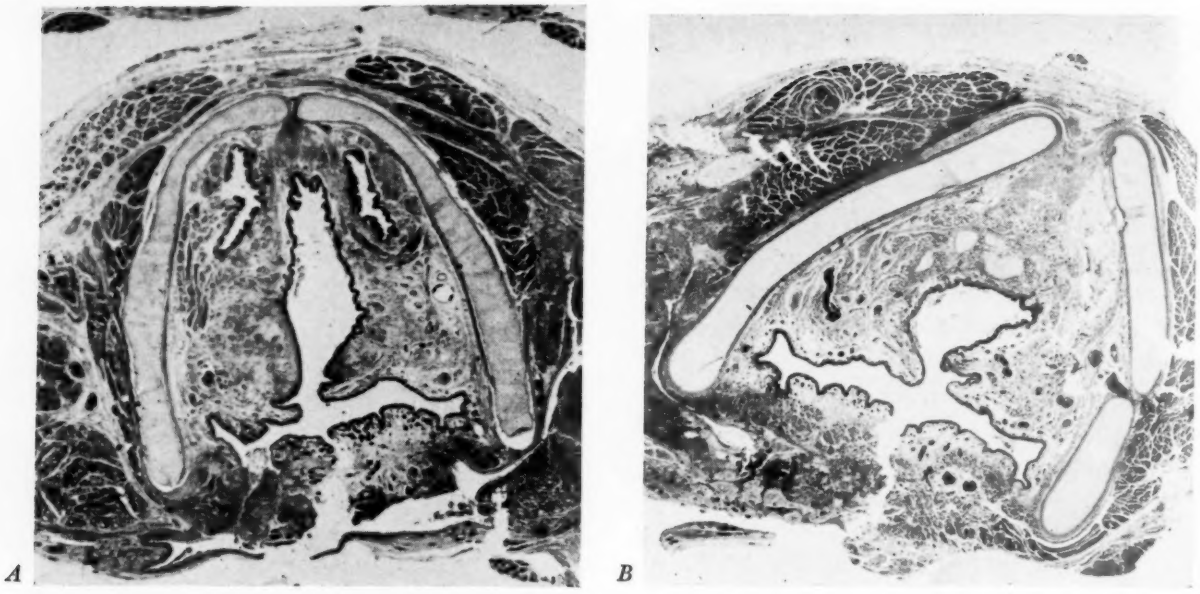

Fig. 3. Photographs of cross sections of the larynx in Case 2. *A*, The region of the vocal chords, *B*, the area a short distance below *A*.

ble to separate the 2 channels within the chest as the first stage of the procedure and then continue from the left side of the neck as described by Petterson for the second stage. A tracheotomy and gastrostomy would be desirable adjuncts.

The observation that the esophageal mucosa extends further forward than the ends of the cartilages of the tracheal part of the tube is important. The extent of the squamous epithelization in such cases is probably very variable. The esophagus and trachea are said to separate when the embryo is about 4 mm. long.[9] The common tube is at first lined by ciliated columnal epithelium and only later becomes squamous.[4] These changes must be early, as Grunwald[2] found. In a tracheoesophageal fistula that he discovered in a 9 mm. embryo, the back of the trachea was lined with squamous epithelium. The presence of such non-ciliated epithelium in a reconstituted trachea would probably be lethal because of the damming-back of bronchial secretions, and in the repair of such a lesion it is probably advisable to make the reconstituted trachea quite small and thus exclude most of the squamous epithelium.

SUMMARY

Three cases of lack of fusion of the posterior larynx and presence of common tracheoesophagus are described. Two of these occurred in siblings. Operation was attempted in one case. The importance of the presence of squamous epithelium extending beneath tracheal cartilage in such instances is stressed with regard to future surgical attacks on this type of lesion.

We would like to express our thanks to Miss Forshall, Mr. P. P. Rickham, and Dr. E. Hall for allowing us to use their case record. The photographs are by Mr. Rickus.

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Apnea and respiratory insufficiency after intraperitoneal administration of kanamycin

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Since Pridgen's[14] initial report in 1956, numerous additional clinical reports have firmly established that neomycin administered intraperitoneally can produce respiratory arrest or insufficiency.[1-3, 8-10, 11, 13, 16, 18] To date reports concerning 18 patients who suffered from this complication have been published. Neomycin was directly related to the death of 4 of these patients. From these reports, several predisposing factors can be identified. Neomycin apnea developed most commonly in children (11 of 18), in whom relative overdosage could easily occur. Except for one patient who received neomycin intrapleurally, all received neomycin in the peritoneal cavity, which permitted rapid systemic absorption. Seven of the 18 had peritonitis at the time of neomycin instillation, which further enhanced systemic absorption.[4, 15] In 16 reports the anesthetic agent used was recorded and in 14 the agent was ether. The pharmacologic mechanism in neomycin apnea has been identified in animals and is the result of a generalized neuromuscular block of the nondepolarizing type identical to that produced by d-tubocurarine.[6, 12] This type of block is potentiated by ether and antagonized by such cholinesterase inhibitors as neostigmine and edrophonium.

Because of this hazard of the intraperitoneal administration of neomycin, especially in children, kanamycin has been substituted for neomycin in this clinic during the past year when a local antibiotic has been used to combat peritoneal contamination. We have recently observed the first instance of neuromuscular block after kanamycin administration in an infant who had been given ether. The block was manifested by general paralysis, including respiratory arrest, and followed by prolonged respiratory insufficiency with recovery. This event is reported because (1) it is believed to be the first recorded instance of neuromuscular block after kanamycin administration, (2) the neuromuscular block did not respond to cholinesterase inhibitors, but was dramatically reversed by a small dose of calcium gluconate, and (3) 4 days after the original operation the infant was anesthetized again by an identical anesthetic technique, and when kanamycin was omitted, postoperative respiratory insufficiency did not occur.

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CASE REPORT

A 3.25 kilogram Negro female infant was born with an imperforate anus and a functioning rectovaginal fistula. Delivery was uneventful, but nasal stuffiness, tachypnea (64 to 80 per minute), and moderate sternal retraction were noted 6 hours after birth and were attributed to atelectasis. On the second day of life, the fistula ceased to function and abdominal distention rapidly developed. The patient was scheduled for surgical repair of imperforate anus on the following day. The hemoglobin concentration was 19.5 Gm. per cent. Electrolyte studies were not performed. The patient was given 0.1 mg. of atropine intramuscularly 30 minutes before induction of anesthesia. Because of the marked abdominal distention and tachypnea before intubation, the infant was given oxygen only by mask without any anesthetic agent. Fifty milligrams of succinylcholine was given intramuscularly and after 2 minutes

the trachea was intubated. Nitrous oxide, oxygen, and ether were then given through an Ayre's system with a Y tube and respiration was assisted. After 30 minutes nitrous oxide was discontinued and ether-oxygen alone was administered.

Since the rectum could not be adequately mobilized from the perineum, the abdomen was opened. This improved ventilation markedly and respiratory assistance was no longer required. After decompression of the bowel, the rectum was mobilized and brought to the perineum. During this time 60 ml. of blood was administered. During abdominal closure a sponge could not be accounted for and a roentgenogram was requested. Ether was discontinued because of the explosion hazard and oxygen alone was given. Shortly after, the infant was observed to move her arms and clench her fists. During the delay for the roentgenogram, approximately 75 mg. of a 0.2 per cent kanamycin solution was instilled into the abdomen. Within 15 minutes and without administration of any other drug or anesthetic, the infant became flaccid and no longer moved or breathed. Blood pressure and pulse did not change. Artificial ventilation was carried out with oxygen and later with nitrous oxide and oxygen for the hour required to complete the operation. The total operative time was 3 hours.

At the end of the operation, the infant remained flaccid. She did not swallow or cough and the corneal reflexes were absent. She made feeble respiratory efforts consisting only of weak diaphragmatic contractions which produced sternal retraction without gas exchange. Artificial ventilation was continued with oxygen through the endotracheal tube and Y-tube system. The abdomen remained moderately distended but less than preoperatively. Rectal temperature was 96.5° F. She was warmed to 99° F. Several attempts were made to allow spontaneous respirations, but each time cyanosis promptly developed. Respirations continued to be diaphragmatic with marked sternal retraction. To eliminate the possibility of airway obstruction, the endotracheal tube was removed, found to be unobstructed, and a new one inserted. One and one half hours postoperatively it was first suspected that kanamycin might have caused the apnea. The infant was therefore given 2.5 mg. of edrophonium (Tensilon) without improvement. A chest roentgenogram was taken to eliminate atelectasis as the cause of respiratory insufficiency. Some atelectasis of the left upper and lower lobes was found. Tracheobronchial aspiration produced some inspissated mucus and with positive pressure ventilation the atelectatic areas were improved. Despite this, the infant remained flaccid, unresponsive, and with inadequate spontaneous respirations. Three hours after operation, a second 2.5 mg. dose of edrophonium (Tensilon) was given, again without improvement.

Approximately 4½ hours postoperatively we recalled the report of Jones,[8] who successfully antagonized neomycin apnea in an infant with calcium gluconate. We therefore slowly administered 200 mg. of calcium gluconate intravenously. Within 1 minute, there was dramatic return of muscle tone and vigorous respiratory efforts. Within 5 minutes the infant began to move, to cough on the endotracheal tube, and to breathe adequately without assistance. An additional 200 mg. of calcium gluconate was given without further change. The endotracheal tube was left in place as a precaution against recurrence of the paralysis. The infant was then placed in an incubator in an oxygen atmosphere and taken to the recovery room 5 hours after operation. No other difficulties were encountered and the endotracheal tube was removed 12 hours after its insertion.

Four days later gangrene of the mobilized rectum was noted. The patient was scheduled for a sigmoid colostomy. The anesthetic management of the second operation was deliberately planned to be the same as in the first operation in order to provide confirmation of the role of kanamycin in the previous respiratory arrest. Except for the smaller degree of abdominal distention, the physical condition of the infant was considered to be the same as it had been prior to the first operation. After premedication with atropine, oxygen was given by mask and 50 mg. of succinylcholine was given intramuscularly. After intubation, nitrous oxide, oxygen, and ether were administered by Ayre's technique with a Y tube, and were gradually converted to ether-oxygen. Respiration was assisted. No kanamycin was given and only 15 ml. of blood was transfused. The operation lasted 1 hour and 25 minutes. The infant was moving with all reflexes and very adequate respirations at the end of operation.

DISCUSSION

The demonstration that neomycin possessed a curare-like action stimulated investigation of the neuromuscular blocking properties of other antibiotics. Iwatsuki and associates,[5-7] using a nerve-muscle preparation in dogs, showed that streptomycin and kanamycin produced a neuromuscular block with characteristics identical to those seen after neomycin administration. They noted that with rapid intravenous administration of neomycin (1 Gm. in 3 minutes) complete paralysis lasting 1 hour was produced,

whereas the same dose administered over a 10-minute period produced no paralysis. With all 3 antibiotics, intraperitoneal instillation produced a greater block than the same dose given intramuscularly. Their data indicate that rapidity of systemic absorption rather than total dose administered was the critical factor in the production of neuromuscular block. In their studies, kanamycin and streptomycin were not as potent (on a milligram per kilogram basis) as neomycin in the production of neuromuscular block. With all three drugs, the block could be reversed by edrophonium. Timmerman and his colleagues,[17] in investigating the neuromuscular blocking effect of a large number of antibiotics, confirmed these results. They found that neomycin, streptomycin, dihydrostreptomycin, polymyxin B, and kanamycin all produced a neuromuscular block in the rabbit sciatic nerve–gastrocnemius preparation. However, kanamycin was less potent than neomycin on a milligram per kilogram basis. In contrast to neomycin and streptomycin, kanamycin and polymyxin produced a neuromuscular block which could not be antagonized by neostigmine.

From both these studies it would seem that kanamycin would be a safer drug than neomycin for intraperitoneal instillation. However, kanamycin can also produce neuromuscular blockade under proper circumstances, such as rapid absorption from the peritoneum in the presence of ether anesthesia. It is likely that this was the mechanism in our patient. Animal data are conflicting as to whether reversal of kanamycin paralysis can be expected from neostigmine or edrophonium. In our patient relief was not obtained with edrophonium, but was dramatic after a small dose of calcium gluconate was given. The nature of the mechanism of antagonism by a small dose of calcium is highly uncertain at this time.

SUMMARY

Kanamycin administered intraperitoneally can produce respiratory arrest or insufficiency identical to that reported to follow the intraperitoneal administration of neomycin. A case is reported in which kanamycin given intraperitoneally produced respiratory arrest in a newborn infant under ether anesthesia. Respiratory insufficiency persisted for 4½ hours postoperatively, was not improved by edrophonium, but was dramatically reversed by calcium gluconate. It was possible to implicate kanamycin further as the probable etiologic agent by reproducing the anesthetic 4 days later. Kanamycin was omitted and respiratory insufficiency did not occur.

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The vascular anatomy of sacrococcygeal teratomas: its significance in surgical management

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The successful surgical treatment of sacrococcygeal teratomas may be jeopardized by excessive blood loss at the time of removal or by the development of local or distant recurrences of the malignant components of the tumors. Most of the reported deaths after attempted surgical extirpation have been due to hemorrhage[1, 4, 6, 8] (Table I). A recent review of the English literature suggests that the incidence of malignancy in such lesions varies from 9 to 23 per cent (Table II). A better understanding of the vascular anatomy of these congenital neoplasms would provide the surgeon with an opportunity to improve management appreciably by enabling him to excise the tumor successfully without undue blood loss or unnecessary dissemination of the tumor during the procedure. Recently we have had an opportunity to study by arteriographic techniques 2 sacrococcygeal teratomas which were seen in newborn infants. A review disclosed no similar studies in the literature.

CASE REPORTS

Case 1. A 5 pound, 2 ounce stillborn white female had a 25 by 19 cm. sacrococcygeal teratoma which had ruptured during a difficult vaginal delivery. At postmortem examination a large middle sacral artery was noted to traverse the pelvis and enter the tumor mass. Arteriographic studies performed on this specimen demonstrated the middle sacral artery to be the sole blood supply of the tumor. Although a thin, freely diffusible contrast medium (50 per cent Hypaque) was used, no reflux into any of the adjacent vessels of the pelvis was noted. Venous drainage occurred centrally through the middle sacral vein. The specimen of the isolated distal aorta showed the middle sacral artery to be comparable in size to the external iliac vessels (Figs. 1 and 2).

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Fig. 1. Case 1. Arteriographic study. Hypaque (50 per cent) was injected via a polyethylene catheter into the middle sacral artery. Although the dye is a thin, freely diffusable liquid, no reflux was noted into vessels of the pelvis. Drainage of the dye occurred centrally through the homologous middle sacral vein.

Case 2. An 8 pound, 5 ounce, 2-day-old white female was admitted to the hospital with a 15 by 15 cm. sacrococcygeal teratoma. At the time of operation, after exposure of the coccyx and transection of the sacrum at the fourth segment, a 4 cm. retrorectal extension of the tumor upward into the pelvis was noted. The middle sacral artery and vein were encountered immediately ventral to the coccyx and were ligated and divided. The tumor and the contiguous coccyx were removed en bloc. Arteriographic studies performed on the isolated specimen through the stump of the middle sacral artery demonstrated this vessel to be the sole blood supply to the tumor and its pelvic extension. The arteries were noted to course to the surface of the tumor where they arborized into a diffuse capillary network. The venous drainage took place centrally through the middle sacral vein (Figs. 3 and 4).

DISCUSSION

Sacrococcygeal teratomas are tumors of more than one germ layer which occur in the region of the coccyx. The pathogenesis remains obscure but most authors believe that they arise from a nidus of multipotential cells which remain at the tip of the involuting tail. Such a theory best fits the clinical observations and is embryologically acceptable since a tail is transiently present in the human embryo during the sixth week of development (Fig. 5). Its blood supply is derived from the middle sacral artery and vein. During the subsequent growth and differentiation there is reabsorption of the tail into its final residual form, the coccyx. The middle sacral artery and vein persist in adults as the blood supply to this rudimentary tail. One would therefore expect

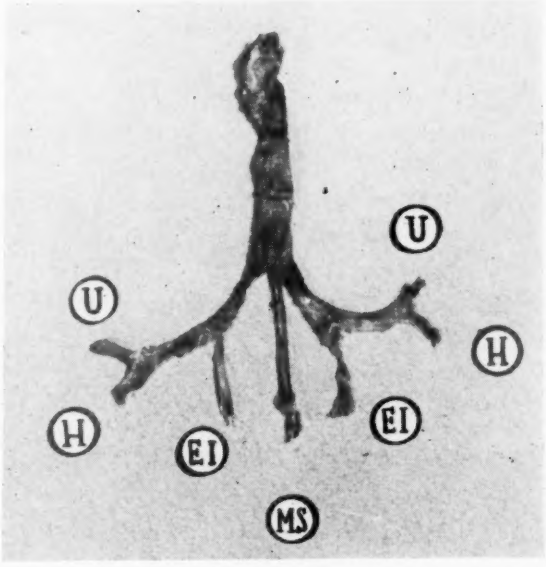
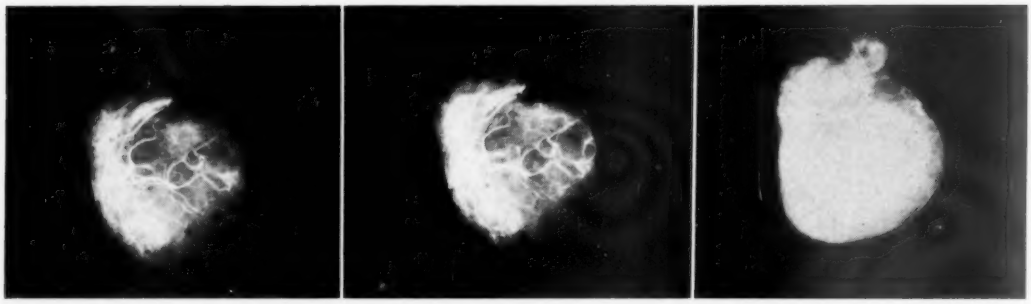


Fig. 2. Case 1. Distal aorta and branches. *U,* Umbilical branch, *H,* hypogastric branch, *EI,* external iliac branch, and *MS,* middle sacral branch. Note huge middle sacral artery. Its diameter is comparable to that of the external iliac arteries.

Table I. *Excessive blood loss during operation*

Author	*No. of cases*	*Author's comments*
Arnheim, 1952	20 per cent operative mortality rate, 10 patients, 2 postoperative deaths, (1 patient, 2 months old, had received 450 ml. of blood)	"These operations are attended by shock and hemorrhage and adequate amounts of blood must be administered during and after operation."
Gwinn and associates, 1955	1 patient in 18 died of shock	No comments
Seindenbergh and Hurwitt, 1958	1 patient with shock during operation	"Blood replacement during resection was insufficient, resulting in shock and rapid termination of the procedure by opening the cyst and cutting across the tumor."
Hoyt and Hardaway, 1960	2 patients with excessive blood loss under the flaps during postoperative period	"As our two cases illustrate, the blood loss is usually greater than even an experienced surgeon realizes. Failure of adequate replacement is the only likely source of mortality."

Fig. 3. Case 2. Tumor at time of operation.



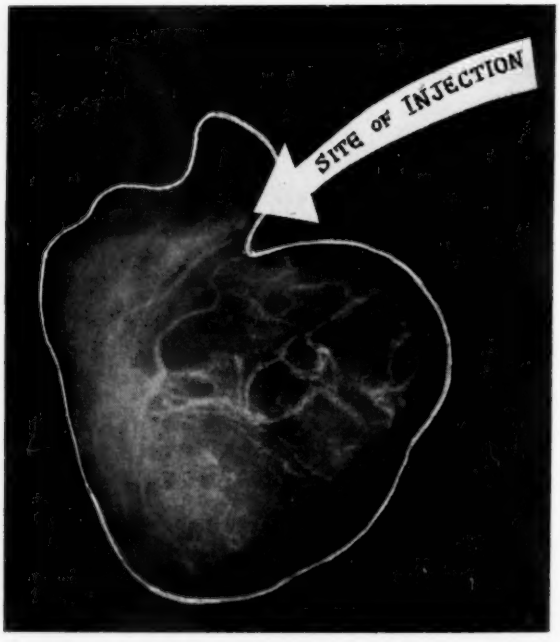


Fig. 4. Case 2. Arteriographic studies of resected specimen. Dye material injected into artery beneath coccyx. Note progressive opacification of specimen and arteries coursing to surface of tumor.

Table II. *Incidence of malignancy*

Author	*Year*	*% reported*
Chaffin	1939	9
Gross, Clatworthy, and Meeker	1951	18
Ravitch	1951	17
Arnheim	1952	20
Hickey and Layton* (review of literature)	1954	20
Gwinn and Dockerty	1955	23

*In a review of 25 cases of proved malignancy, 16 patients were older than 4 months at the time of operation.

the blood supply to a teratoma arising in this region to be derived from these vascular elements.

As surgical lesions, sacrococcygeal teratomas may be broadly classified into two types, (1) tumors growing outward from the region of the coccyx with little or no pelvic extension, and (2) those growing inward from the region of the coccyx with large pelvic and occasional intra-abdominal extensions.

Fortunately, the majority of sacrococcygeal teratomas are of the first type. The surgical management has varied little since the first successful resection by Blizzard. The most popular current surgical technique has been that described by Gross and associates[3] who place the patient in a prone position with the hips elevated and initiate the dissection with an inverted v-shaped incision made over the buttocks (Fig. 6). Wide skin flaps are developed as the dissection is carried laterally around the tumor mass. The coccyx is resected late in the operation after the bulk of the peripheral dissection has been completed. Such a technique has 3 disadvantages. There may be excessive blood loss from the extensive peripheral dissection of the soft tissue surrounding the tumor prior to ligation of the central pedicle to the tumor, neoplastic cells may be spread during the excessive manipulation of the tumor mass prior to the ligation of the middle sacral vein, and exposure of the rectum and intrapelvic portion of the tumor is delayed and difficult.

Inasmuch as the vascular supply of sacrococcygeal teratomas appears to be limited to the sacrococcygeal artery and vein, it appears logical to recommend a modification of this surgical approach for such lesions (Fig. 7).

If the tumor is an external one with little or no pelvic extension, the patient is placed in the usual prone position and through the conventional inverted v-shaped incision, the dissection is carried down at the apex of the incision to expose the coccyx. The sacrum can then be divided at the fourth or fifth sacral segment. The middle sacral artery and vein, located immediately ventral to it, are ligated and divided. The skin flaps are developed around the tumor and the mass is removed en bloc with the coccyx. Such a procedure provides prompt hemostasis, prevents tumor spread, and allows for early adequate exposure of the rectum.

For tumors with large retrorectal extensions into the pelvis and abdomen a single two-stage operation is recommended (Fig. 8). The first step is completed through a midtransverse suprapubic incision, at which time in most cases an extraperitoneal dissection can be carried downward to the origin of the middle sacral artery and vein which are then ligated and divided. The intrapelvic extensions of the tumor can then be dissected free without excessive blood loss. The

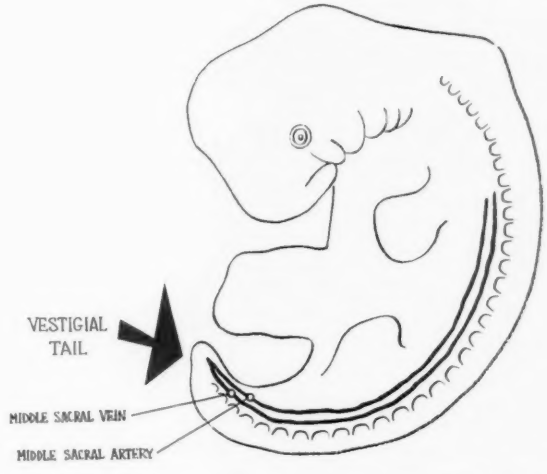


Fig. 5. Human fetus at 6 weeks. A tail is transiently present at this time. Its blood supply is derived from the middle sacral artery and vein.

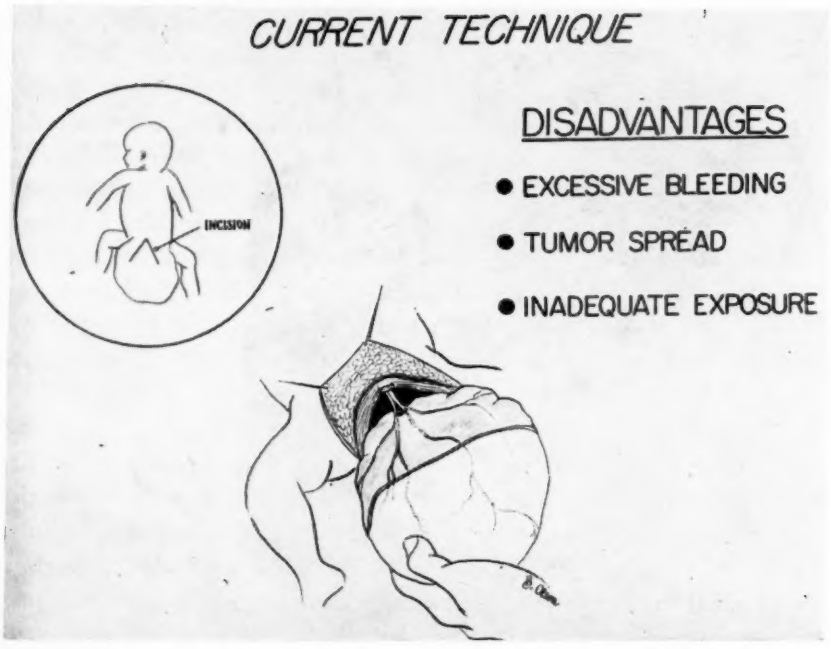


Fig. 6. Current technique. Skin flaps are widely dissected and tumor is mobilized. Vascular pedicle is yet to be ligated.

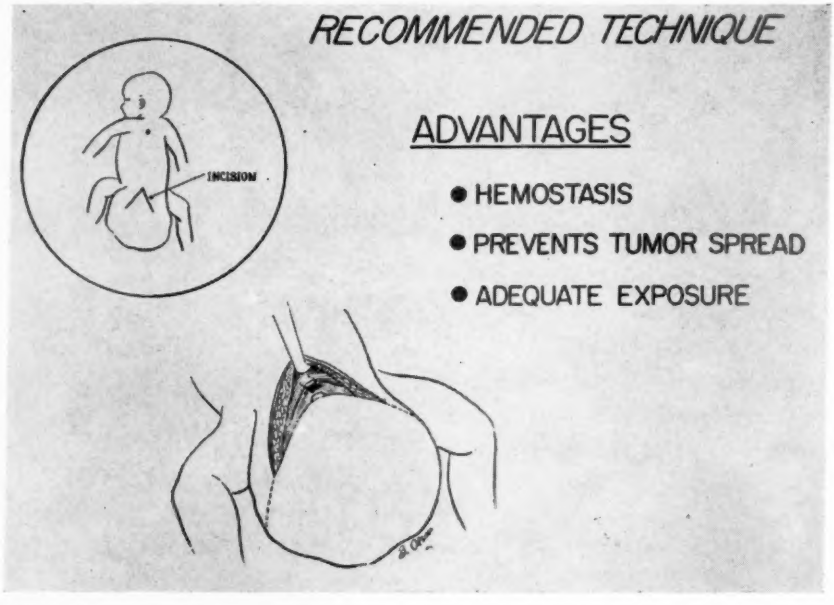


Fig. 7. Recommended technique. Coccyx is divided and middle sacral artery and vein are ligated. There has been no tumor manipulation.

abdomen is then closed. The patient is turned over and the usual inverted v-shaped incision is made over the region of the buttocks. The sacrococcygeal area is exposed and the entire tumor is removed from below.

For such combined lesions this approach has 4 advantages, (1) both steps can be accomplished in a single operation, (2) pelvic exposure is excellent, (3) hemostasis is secured early in the procedure, and (4)

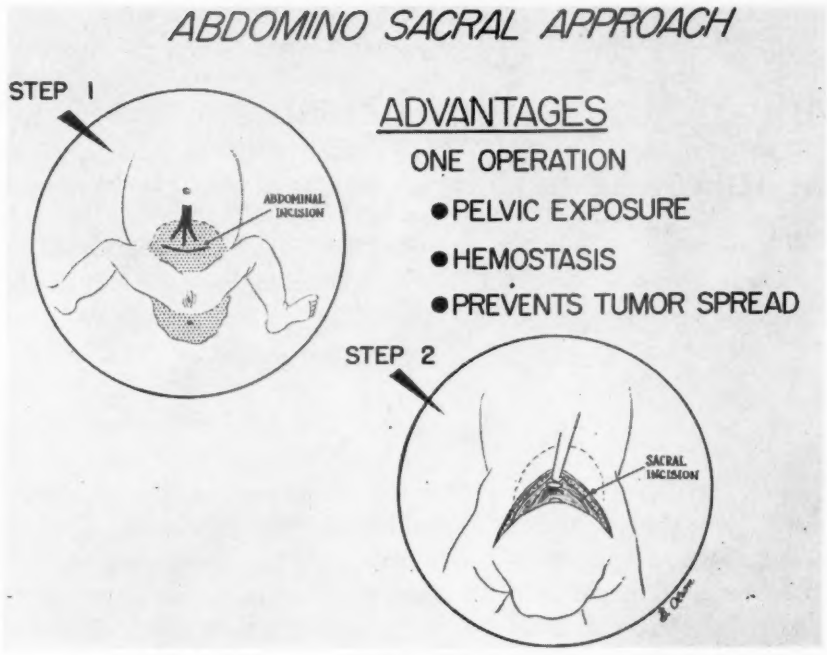


Fig. 8. Abdominosacral approach. The middle sacral artery is approached extraperitoneally through the transverse suprapubic incision. Intrapelvic extensions are dissected free at this time. The patient then is placed in a prone position and the usual sacral approach is carried out.

tumor spread is prevented insofar as possible. Ligation of the main vessels prior to the prolonged manipulation of the tumor would be in keeping with the well-established principles of cancer surgery. All sacrococcygeal teratomas are approached as though they were malignant and early ligation of the vascular venous pedicle is achieved.

SUMMARY

The reported deaths after the removal of sacrococcygeal teratomas have been largely due to hemorrhage and recurrent malignancies. Present techniques for the surgical excision of these tumors do not adequately emphasize the importance of the vascular anatomy of sacrococcygeal teratomas, as has been demonstrated in 2 cases reported. These anatomic studies suggest that excessive blood loss and contamination of the blood stream by cancer cells can be avoided by ligation of the middle sacral artery and vein prior to the mobilization and removal of these tumors.

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Recent advances in surgery

Conducted by ALFRED BLALOCK, M.D.

Re-evaluation of the surgical treatment of duodenal ulcer

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The effectiveness of any operative procedure designed to control the complications of duodenal ulcer can be determined only through experience with a relatively large series of patients with follow-up over an appreciable number of years. The aim of definitive surgical treatment for duodenal ulcer is to eliminate the ulcer and its tendency to recur and at the same time to produce a low operative mortality rate and few unpleasant postoperative sequelae. From the turn of the century up to the late 1930's, simple gastroenterostomy was used almost exclusively in this country as definitive surgical treatment for duodenal ulcer. The procedure has now been abandoned almost completely, as the recurrence rate has varied from 10 to 50 per cent. During the past 15 years, several other surgical procedures have undergone extensive clinical trial in the treatment of duodenal ulcer. Each, when properly performed, has provided a means of relief of the ulcer diathesis. All have been directed toward reducing the excessive acid-peptic secretions of the stomach to normal or subnormal levels. Undoubtedly the most widely used of the procedures is "adequate" subtotal gastric resection. A second method used extensively by a few groups is segmental resection of the acid-secreting area of the stomach, with preservation of the vagi and gastric antrum. A third operation is vagotomy combined with either gastroenterostomy or pyloroplasty. A fourth approach has been subdiaphragmatic vagotomy coupled with removal of the gastric antrum.

Adequate subtotal gastric resection. Although subtotal gastric resection of the Billroth II type (Fig. 1), or one of its modifications, is still the method most widely employed to control ulcer disease, there can be no doubt of the fact that in recent years the procedure has lost some of its universal appeal. Other operative procedures of less magnitude are proving to be equally or more effective in controlling the complications of duodenal ulcer. Also, some of the latter procedures appear to be founded on more sound physiologic principles. It is generally accepted that for subtotal gastric resection to be effective in reducing acid-peptic activity to a minimum, at least 70 to 80 per cent of the stomach should be removed. Less extensive resections are associated with a high rate of recurrent ulceration. Likewise, resections of "adequate" extent have not been completely successful in eliminating the problem of recurrence. To be considered also are the undesirable postoperative sequelae, such as excessive weight loss, nutritional problems, and postprandial symptoms, which occur in a sizable percentage of patients after adequate subtotal gastrectomy.

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Smithwick[14] has recently noted a recurrence rate of 5.7 per cent among 458 patients with follow-up of from 1 to 13 years. The Lahey Clinic[9] mentions a recurrence rate of 4 per cent in 2,200 patients. Walters[16, 17] found a 4 per cent recurrence rate among male patients and 5 per cent rate in females. Woodward[23] mentions a recurrence rate of 9.1 per cent among 253 patients. The operative mortality rate in large surgical centers after subtotal resection has varied from 1.5 to 4 per cent.

Gastric resection of the Billroth I type without vagotomy (Fig. 2), performed for duodenal ulcer, has been associated with a recurrence rate varying from 5 to 30 per cent.[11, 18, 19] It appears to be the general opinion at the present time that this procedure is unsatisfactory as a mode of therapy to control the ulcer diathesis. The operation, however, has proved extraordinarily effective in the management of benign gastric ulceration.

Segmental gastric resection. Segmental gastric resection (Fig. 3), as advocated by Wangensteen,[2, 20, 21] consists of an extensive resection of the body and fundus of the stomach with preservation of the gastric antrum and concomitant pyloroplasty. The physiologic basis for the operation is the extirpation of a large portion of the acid-bearing mucosa, with inhibition of the antral phase of gastric secretion produced by the residual acid-secreting cells high in the gastric fundus. The original procedure has been modified by Ferguson[6] to preserve innervation of the antral segment and thus avoid pyloroplasty, on the assumption that a normally functioning antrum and pylorus might alleviate postgastrectomy symptoms. However, the latter modification has produced results approximately equal to those obtained with "adequate" distal gastric resection. The recurrence rate after segmental resection has been approximately 4 per cent. The procedure has definite disadvantages in that it entails an extensive extirpation of the gastric reservoir and it is not an ideal operation for the patient who has massive hemorrhage or an acute perforation. Also, the procedure

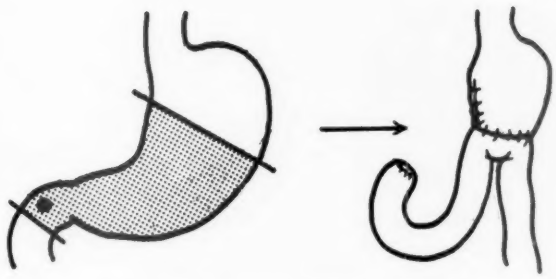

Fig. 1. Adequate subtotal gastric resection (Billroth II).

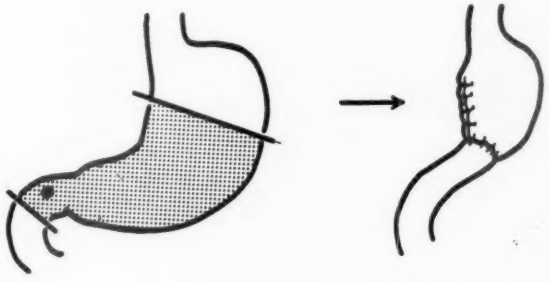

Fig. 2. Subtotal gastric resection (Billroth I).

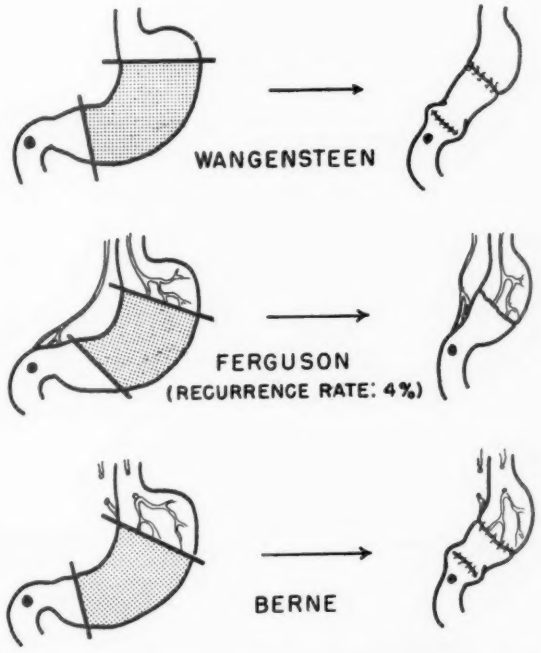

Fig. 3. Segmental gastric resection.

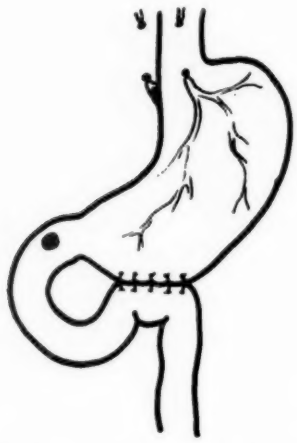

Fig. 4. Vagotomy and gastroenterostomy.

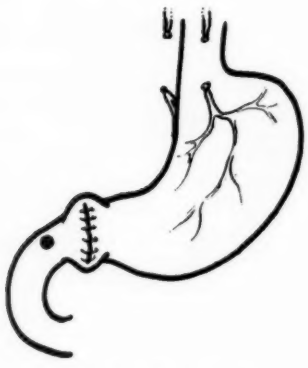

Fig. 5. Vagotomy and pyloroplasty.

is not applicable to the patient with complete pyloric obstruction. An additional undesirable feature has been postoperative substernal discomfort suggestive of reflux esophagitis, which may be attributable to the presence of a small gastric reservoir and straightening of the cardioesophageal angle. A somewhat similar operative procedure, consisting of supra-antral segmental resection with vagotomy and pyloroplasty, has been utilized by Berne.[1] Satisfactory results have been obtained over a short follow-up period in certain selected patients.

Vagotomy and a drainage procedure. Vagotomy and gastroenterostomy (Fig. 4) received widespread initial support by certain groups after its introduction by Dragstedt. The subsequent decline in enthusiasm for the procedure, however, is a story well known to surgeons interested in gastric disease. At the present time there appears to be renewed interest in the operation, particularly in its application in certain selected cases. The attractive features of vagotomy and gastroenterostomy are the technical simplicity and low operative mortality rate (0.5 per cent). The operation, however, has been associated with an appreciable rate of recurrent ulceration. Walters[16] found a recurrence rate of 13 per cent among 124 patients. Edwards[4] reported a recurrence rate of 13.3 per cent in 147 patients. Among a large group of 724 patients studied by Dragstedt and Rigler,[3] the recurrence rate was 10.6 per cent. Grimson[7] mentions a 4 per cent rate of recurrence among 282 patients.

Vagotomy with pyloroplasty (Fig. 5), as advocated by Weinberg[22] and Farris,[5, 13] is a physiologically similar operation based on the elimination of the cephalic phase of gastric secretion by vagotomy and the prevention of antral stasis by a properly performed pyloroplasty. The supporters of the operation maintain that pyloroplasty is superior to a properly placed gastroenterostomy and that it will nullify the antral phase of secretory activity just as effectively as antral extirpation. The procedure, however, has not yet received sufficient clinical trial to warrant such comparison. Through 1959, Weinberg had performed vagotomy and pyloroplasty on 827 patients. Every third patient in this large group was thoroughly studied postoperatively and the recurrence rate among approximately 300 patients was 5 per cent.

Both of the operations described appear to be less effective in preventing recurrent ulceration than some of the other procedures in current use today. However, some believe at present that because of the low operative mortality rate associated with vagotomy and gastroenterostomy or pyloroplasty, these procedures are the choice for the patient with the complications of duodenal ulcer. Others think the operations are only indicated for certain patients, such as the geriatric patient with complications of ulcer, the poorly

nourished and underweight patient, and patients who present technical problems which are too dangerous to warrant resection.

Vagotomy and antral resection. Vagotomy and hemigastrectomy was apparently first performed by Smithwick[14] in 1946. A few months later Edwards independently described a similar operative procedure, consisting of vagotomy and a distal 40 per cent resection. The portion of stomach removed was termed an "antrectomy" (Fig. 6). Both procedures appeared to be a physiologic approach to the problem of duodenal ulcer aimed at eliminating the two main phases of gastric secretion, namely, the cephalic and humoral, which are mediated through the vagal pathways and by the antral mucosa, respectively. The role of the vagal pathways in the perpetuation of ulcer disease is established by sound experimental and clinical observations. The role of the gastric antrum in the genesis of ulcer disease is not as well understood. However, there is convincing experimental and clinical evidence to suggest that it plays an important role.

The combined operation of vagotomy and antral resection has had widespread clinical application during the past decade, and there is evidence to show that it is proving extremely effective in providing a means of relief of the ulcer diathesis. The operation has the advantage of being applicable to the patient with any of the complications of duodenal ulcer. Its use is not restricted to those who undergo an elective operation. During the past several years on our services, we have become extremely interested in the satisfactory results which have been obtained by a combination of vagotomy and antrectomy in the treatment of duodenal ulcer.

CLINICAL MATERIAL

During the past 13½ years, a total of 832 patients have undergone vagotomy and antral resection in the surgical treatment of duodenal ulcer. The group includes both private and staff patients operated upon by members of the surgical service at Vanderbilt University Hospital, private patients of the Edwards-Eve Clinic, and patients from the surgical service of the Thayer Veterans Administration Hospital, Nashville, Tennessee. All patients were treated by a subdiaphragmatic vagotomy and estimated 40 to 50 per cent distal gastrectomy.

The age range was from 15 to 81 years, with the average age at the time of operation being about 46 years. The series consists of 685 men and 147 women, or a ratio of 4.7 to 1.

The indication for operation in this group was chronic duodenal ulcer and its complications, except in a small group of patients who underwent operation for sudden massive hemorrhage or acute perforation as the initial manifestation of ulcer.

The duration of ulcerlike symptoms for the entire group of 832 patients ranged up to 40 years, with an average of 11 to 12 years.

Pain not responding to medical management constituted the chief indication for operation in 52 per cent of the entire group. Recurrent or massive hemorrhage was the reason for operation in 29 per cent. Seventeen per cent of the patients had pyloric obstruction which required surgical correction and a small group of 2 per cent underwent operation for an acute perforation

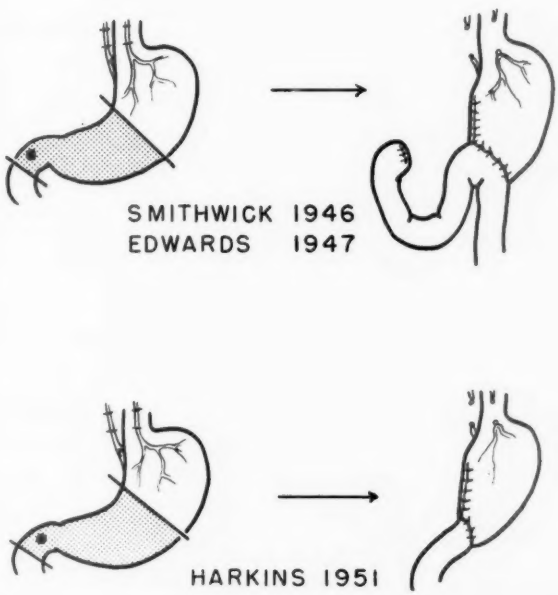

Fig. 6. Vagotomy and antral resection.

Table I. *832 patients with vagotomy and andrectomy*

	Billroth I	*Billroth II*	*Totals*
Men	282	403	685
Women	89	58	147
Totals	371	461	832

Table II. *Mortality data*

No. of patients	*Indication for operation*	*Cause of death*
12	Massive hemorrhage	Cardiac or pulmonary complications (7), suture line leaks (3), acute pancreatitis (1), pseudohemophilia (1)
5	Pyloric obstruction	Cardiorenal disease (3), pulmonary embolus (1), subphrenic abscess (1)
6	Pain	Postoperative hemorrhage (1), acute pancreatitis (1), cardiac arrest (1), subphrenic abscess (1), suture line leaks (2)

Table III. *Delayed gastric emptying*

	No. cases	*Reoperation*
Billroth I	17	9
Billroth II	16	6

(Fig. 7). Among the group of 832 patients subjected to vagotomy and antrectomy, 371 had a Billroth I (gastroduodenostomy) anastomosis, while 461 had a Billroth II (gastrojejunostomy) type of reconstruction (Table I).

There were 23 hospital deaths (a mortality rate of 2.7 per cent) in the 832 patients. Among the 23 deaths, 12 or 52 per cent occurred in patients who had undergone emergency operation for the control of massive hemorrhage. Ten of the 12 patients were in the seventh or eighth decade of life and the surgical risk for each had been considered poor when they were first observed.

Seven of the patients died with cardiac or pulmonary complications in the early postoperative period. A duodenal stump or anastomotic leak accounted for 3 deaths, acute pancreatitis for 1, and 1 patient with pseudohemophilia died from uncontrollable hemorrhage.

Five of the 23 deaths occurred in patients who had undergone operation for pyloric obstruction and 3 of the 5 deaths were due to cardiorenal complications. One patient had a massive fatal pulmonary embolus, and another died from a subphrenic abscess. The causes of death in 6 other patients were postoperative bleeding from a pancreatic cyst excised at time of vagotomy and antrectomy, acute pancreatitis, cardiac arrest, subphrenic abscess, and, in 2 patients, leakage from the duodenal stump (Table II).

If the 12 patients who died after emergency operation for control of massive hemorrhage are excluded, the mortality rate is reduced to 1.3 per cent.

The major nonfatal complication after operation related directly to the gastric operation per se was delayed gastric emptying. This occurred in 33 patients and in 15 of these reoperation was necessary. There was no significant difference between the Billroth I and Billroth II types of reconstruction with regard to the incidence of this complication (Table III).

RESULTS

Among the 832 patients who underwent vagotomy and antral resection from January, 1947, through June, 1960, it has been possible to assess the current status of 827 patients (99 per cent). Twenty-three patients died in the hospital after operation. Five other patients have been lost to follow-up over the years. Twenty patients have subsequently died of unrelated causes during the follow-up period, but were followed to the time of their death. Therefore, 804 patients have been observed for periods extending from several months to 13½ years. The majority of the 804 patients have been examined repeatedly by members of the staff. In a few instances, follow-up studies have been ob-

tained through the referring physician. The patients who underwent a Billroth II reconstruction have been followed since 1947, and approximately one-half of the group have been observed for at least 5 years. The Billroth I patients have been followed for a shorter period, but about one-half of this group have been observed from 2 to over 5 years, with the longest follow-up being over 8 years.

A critical appraisal has been made of the clinical results among the 804 patients. To be graded as having an "excellent" result, the patient must be entirely free of symptoms referable to the gastrointestinal tract. No dietary restrictions must persist and the patient is likened to an individual with a normally functioning gastrointestinal tract. The patient with "good" results has excellent gastrointestinal function, but occasionally notes mild dumping, fullness, or mild diarrhea. The patient with "fair" results has received decided benefit from operation without residual ulcer symptoms, but notes moderate dumping, diarrhea, or abdominal discomfort at times. Patients with "poor" results are individuals with objective or subjective evidence of recurrent ulcer, those who have not received benefit from operation, and patients with nutritional difficulties and postgastrectomy symptoms severe enough to interfere with their occupations.

Five hundred forty-one patients have been listed as obtaining an excellent result, whereas 216 patients obtained a good result. Thus, 93 per cent of the patients were judged to have excellent and good results after operation. Twenty-nine patients were classified as having fair and 18 as having poor results (Fig. 8). The latter category includes 5 patients who developed recurrent ulceration. There was no significant difference in the results as classified according to the type of gastrointestinal anastomosis. Ninety-three per cent of patients with a Billroth I reconstruction were graded as having good or excellent results, whereas 94 per cent of the Billroth II group were similarly classified (Fig. 9). Fig. 10 shows the length of follow-up among the 804 patients.

Among the 804 patients, postprandial symptoms have been experienced by 26 per cent of the entire group (Fig. 11). The symptoms were classified as "mild," "moderate," or "severe." In many instances, reports

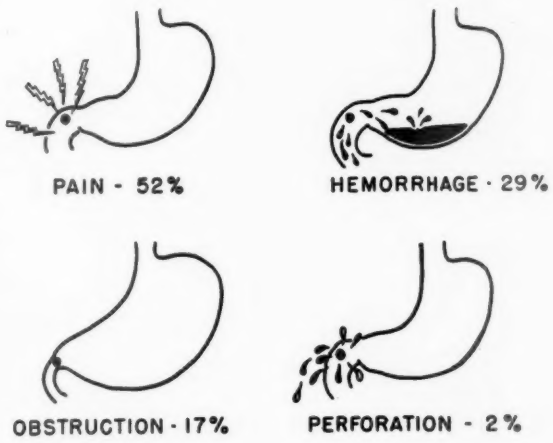

Fig. 7. Indications for operation.

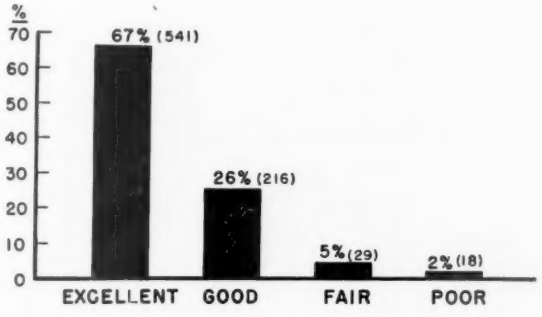

Fig. 8. Results.

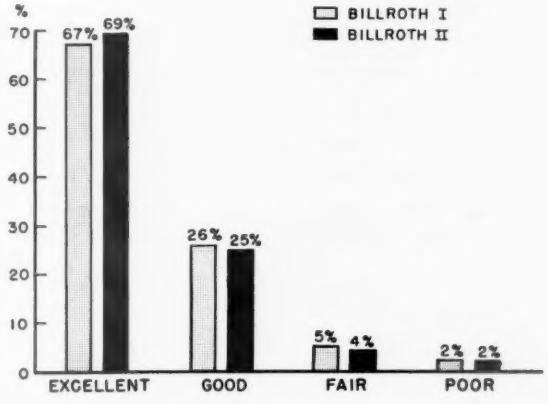

Fig. 9. Results according to type of gastrointestinal anastomosis.

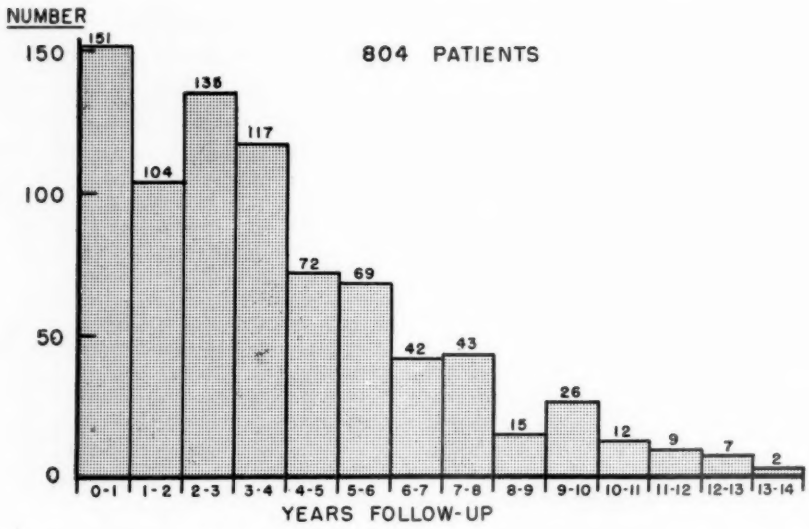

Fig. 10. Length of follow-up.

of mild dumping symptoms could be elicited only upon careful questioning of the patient and, in general, these symptoms have not been a source of distress to either the patient or physician. Twenty per cent of the entire group experienced mild dumping symptoms. Symptoms of moderate degree were noted by 4.5 per cent, and for the most part have been controlled by dietary and instructive measures. Four patients have been classified as having severe dumping symptoms. Two of the 4 have since undergone reoperation with conversion of the Billroth II gastrojejunostomy to a Billroth gastroduodenostomy with marked relief of symptoms. A third patient underwent revision of his gastrojejunostomy with improvement. A fourth patient with severe dumping has not responded to nonoperative measures.

An evaluation of the preoperative and current weight status was obtained on 715 of the 804 patients. Six hundred four patients have maintained their ideal weight since the operation, while 71 patients have lost 10 per cent or more of their ideal weight. Forty patients have gained 10 per cent or more over their ideal weight. Postoperative anemia has been but rarely encountered in the entire group of patients (Fig. 12).

Recurrent ulceration. Five patients among the group of 804 have developed a recurrent ulceration (incidence of 0.6 per cent) during the follow-up period (Fig. 13).

Two recurrences took place in patients who underwent a Billroth I reconstruction after vagotomy with antrectomy. One of these occurred in a 57-year-old woman who originally had undergone a simple gastroenterostomy elsewhere for an obstructive duodenal ulcer. Eight years later she was subjected to vagotomy, antrectomy, and a Billroth I reconstruction for a large marginal ulcer. Eight months after operation she was readmitted to the hospital, having recently suffered a massive hemorrhage. At reexploration an ulcer crater was found on the posterior wall of the second portion of the duodenum. A gastric re-resection was performed, but because of her condition at the time of operation, the periesophageal area was not explored for the possibility of finding an intact vagal nerve trunk. The pancreas, however, failed to reveal an adenoma. She has had no further trouble over a 3½-year follow-up.

The second recurrence after a Billroth I reconstruction took place in a 63-year-old man, who developed epigastric distress 14 months after operation. The 12-hour fasting gastric secretory studies showed 80 mEq. of free hydrochloric acid and roentgen study demonstrated a large ulceration at the site of the gastroduodenostomy. At reoperation

a malignant Zollinger-Ellison islet-cell tumor of the pancreas was encountered.

The other 3 recurrences were in patients who had undergone a posterior Hofmeister reconstruction after vagotomy with antrectomy. One of the recurrences took place in a 44-year-old man 2 years after the original operation. The result of an insulin test was positive and the free hydrochloric acid was 112 units. At transthoracic exploration an intact vagal nerve fiber was found extending to the stomach. Unfortunately the patient developed mediastinitis and an esophageal fistula, which proved fatal.

The second recurrence after a Hofmeister reconstruction occurred in a 54-year-old man 10 months after operation. A marginal ulcer was demonstrated radiographically and at reoperation an intact vagal nerve fiber was found and divided. The pancreas appeared normal and exploration of the duodenal stump demonstrated no retained antral tissue. The patient has been followed for almost 1 year since reoperation and has had no further difficulty.

The third recurrence after a Hofmeister anastomosis recently became manifest. It occurred in a 56-year-old woman, who developed abdominal fullness, nausea, and vomiting 2 months after vagotomy and antrectomy. Roentgen study demonstrated gastric retention and a poorly functioning stoma. The free hydrochloric acid was 40 clinical units and the nocturnal gastric secretion showed 42 mEq. of free hydrochloric acid. At reoperation a large obstructing ulcer was found in the efferent limb of the jejunum 2 cm. below the gastroenteric stoma. The pancreas appeared normal and no antral tissue was found attached to the duodenum. A large vagal trunk was demonstrated to the right of the esophagus and this was divided. The ulcer was resected and the stoma revised. An interesting feature in this case was that at the time of the original vagotomy 2 large nerve trunks and 3 small accessory fibers had been found and divided. The patient has had no further difficulty during a short follow-up period (Fig. 13).

DISCUSSION

Vagotomy with antral resection has provided extremely effective therapy for the complications of duodenal ulcer in our experience to date.[8, 12] The results have been superior to those obtained in patients who were subjected to adequate subtotal resection

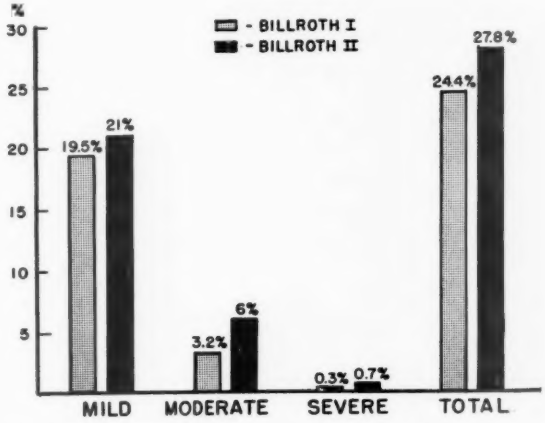

Fig. 11. Dumping syndrome.

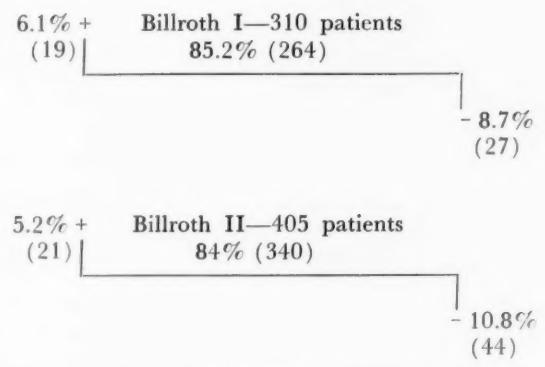

Fig. 12. Postoperative weight status of 715 patients.

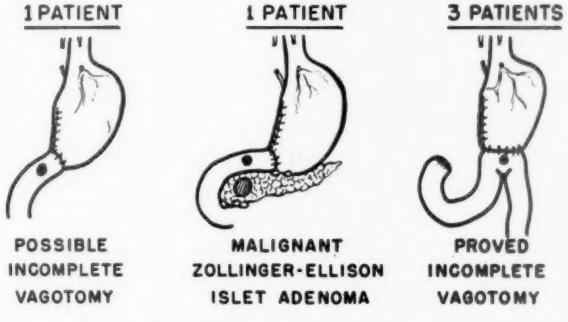

Fig. 13. Recurrent ulceration (5 recurrences among 804 patients, an incidence of 0.6 per cent).

and to those achieved in patients who have undergone vagotomy with a drainage operation. Ninety-three per cent in this series of 804 patients have obtained excellent to good results over varying periods of up to 13½ years. Similar experiences have been reported by others who have utilized the combined procedure.[10, 15]

One of the chief objections to vagotomy and antrectomy is that the procedure has not been employed for a sufficient length of time to accurately determine recurrence rates. The series presented in this study, along with recent reports of others, give strong evidence to the contrary. Another objectionable feature of vagotomy and antral resection has been the mortality rate, which has varied from 2 to 3 per cent in most reported series. Admittingly, this rate is somewhat high, but it compares favorably with the mortality rate after adequate subtotal resection. Also, it should be stressed that the series in this study largely represented consecutive patients, and only recently has consideration been given to the employment of an operative procedure of less magnitude in certain patients with poor risk and in elderly individuals. Twelve of the 23 operative deaths in this study were in patients who were operated upon as an emergency for the control of massive hemorrhage. Ten of the 12 patients had coexisting constitutional disease and each of the 12 presented an extremely poor operative risk. It should be pointed out that reports concerning the mortality rate after vagotomy and a drainage operation usually do not include patients with massive hemorrhage. Recently, in an attempt to reduce the mortality rate, vagotomy with a drainage operation has been used in lieu of antral resection in certain patients, including the elderly patient who presents a poor risk, the poorly nourished and underweight patient, and individuals who present difficult technical problems which contraindicate resection. In certain instances of massive bleeding in the elderly and poor-risk patients, we have utilized vagotomy and a drainage procedure combined with transduodenal ligation of the bleeding vessel.

There has been no appreciable difference in the over-all excellent and good results among the Billroth I and Billroth II groups (93 and 94 per cent, respectively). Excessive weight losses have not been a problem, and only rarely has a case of postoperative anemia been encountered. No doubt this is due to the fact that an adequate gastric reservoir is preserved.

Symptoms of the dumping syndrome have occurred in 26 per cent of the 804 patients. In the majority of cases, the symptoms have been mild and usually transient. In only 4 patients have postprandial symptoms been of extreme severity. It is important to instruct each patient carefully on a planned postgastrectomy dietary regime before discharge from the hospital. A diet high in protein and fat content, but low in carbohydrate, is stressed. Patients are told to abstain from liquids with their meals and for 30 minutes to 1 hour after eating. Usually after a period of 6 weeks the patient's tolerance to carbohydrates is assessed and the dietary regime relaxed. A normal diet with few restrictions is then enjoyed by most of the patients.

Vagotomy and antral resection appears to afford an extraordinary degree of protection against the development of recurrent ulceration. This is one feature which has been emphasized by others who have reported large series of cases. Patients have now been followed for over a decade and the protection against recurrent ulceration appears to exceed that afforded by adequate subtotal resection. Five patients (0.62 per cent) among 804 in this series have developed recurrent ulceration to date. Three of the 5 were proved at reoperation to have had incomplete gastric denervation. A fourth patient probably had an incomplete vagotomy. The fifth patients was found to have a malignant islet-cell pancreatic tumor at re-exploration. It is of interest that each of the 5 recurrences took place within 24 months after vagotomy and antral resection. This is in contrast to recurrences after vagotomy and a drainage operation, which may take several years to occur. At present the recurrences

after vagotomy and antral resection have not increased with the passage of time and complete achlorhydria is still present in the patients tested as long as 10 to 13 years postoperatively.

SUMMARY

At present there are at least 4 operative procedures generally used to control the complications of duodenal ulcer, namely, adequate subtotal resection, supra-antral segmental gastrectomy, vagotomy combined with a drainage procedure, and vagotomy with antral extirpation.

The advantages and disadvantages associated with each of the operations are briefly outlined, along with the general over-all results obtained with each procedure.

Emphasis is placed on the utilization of vagotomy and antral resection as the procedure of choice for the majority of patients who undergo operation for control of the complications of duodenal ulcer.

Indications are cited for the use of an alternate operative procedure in selected instances.

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Surgical history

Conducted by JOHN R. PAINE, M.D.

Dr. Donaldson and the lost "Reading" bacillus

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Although World War I, World War II, and the intervening and subsequent historical and political events seem to have emphasized the futility of war as a method for resolving modern international differences, these conflicts have compensated partly for the sacrifices they have imposed upon mankind by accelerating advances in medicine and surgery. The era of World War I may well be the most interesting and significant of any period of comparable duration in the history of medicine and surgery. The British medical literature of this period is particularly fascinating, yet the current generation of American physicians and surgeons, especially the younger ones, seems to be almost completely unaware of most of the heritage which has resulted from the medical problems, controversies, and personalities generated by World War I. It is unfortunate that medical practitioners tend to forget many of the lessons learned in war and to drop certain advances and discoveries which resulted in expedient solutions to major wartime problems because they do not seem applicable to peacetime practice.

An informal canvass of about 50 American medical graduates of the past 15 years showed that not a single one remembered or apparently had ever heard of the "salt-pack" method for treating gunshot wounds, and only 1 or 2 vaguely recalled something of Sir Almroth Wright,[1,2] who was largely responsible for the rather widespread use of this method during World War I. Yet this method of Wright's was an important transition between the Listerian concept of treating wounds with antiseptics and the modern method of treating them by gentle but adequate cleansing and débridement. A controversy regarding the salt-pack method and its originators raged in the medical literature for practically the entire duration of World War I. The vituperative characteristics of the feud between the proponents and the opponents of Sir Almroth's method may be illustrated by the devastating remark credited by Cushing[2] to H. H. Bashford to the effect that the only difference between Wright and wrong lay in the W.

If few recall Sir Almroth and the salt-pack method, even fewer must recall Dr. Robert Donaldson and the "Reading" bacillus. The relationship between Wright's method and Dr. Donaldson's "Reading" bacillus rests with a surgeon, Major J. Leonard Joyce, R.A.M.C.(T.), who was an advocate and user of the salt-pack method for the treatment of gunshot wounds at the War Hospital, Reading, Berkshire. Major Joyce observed that the wounds which were treated successfully by this method developed a characteristic foul, pungent odor which was absent when the treatment failed. At this time the salt-pack method, as practiced by Joyce, consisted essentially of packing the wounds as tightly as possible with gauze packs which had been soaked in hypertonic saline and leaving this dressing in place for approximately 6 days.

When he was consulted by Joyce, Donald-

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son concluded that the evil odor emanating from the war wounds which were healing well probably was caused by an anaerobic micro-organism, and he succeeded in culturing 2 anaerobic bacteria from the wounds.[6] One of these organisms formed round terminal spores in small numbers, whereas the other formed large, oval subterminal spores in large numbers. Meat-broth cultures of these organisms showed active proteolysis and emitted the same powerful odor as had the wounds from which they were obtained. Using the methods which he previously had reported,[5] Donaldson apparently succeeded in isolating the organism which formed the large, oval subterminal spores, and he found that apparently pure cultures of this organism still emitted the characteristic odor. He concluded that this organism probably was the sole agent responsible for cleansing of the wounds which did well under the salt-pack treatment, and that it was absent from wounds which remained refractory to this treatment and reacted as though an antiseptic, instead of salt, was used upon them.

Donaldson injected the bacillus into animals without causing gangrene. He also used it extensively with excellent results and without untoward effects in the treatment of war wounds of horses and mules. Continuing to use the salt-pack treatment, Donaldson and Joyce then began to sow the organism generously in the wounds, including those of the knee and other joints, of soldiers under their care in the Reading War Hospital. Donaldson states that this practice, "always with the best results," never led to any pathogenic effects but invariably to a rapid cleansing of the wounds.[3] He declared that the bacillus acted by "proteoclastic enzymes which hydrolyze the substrate of dead proteins," that it thereby disintegrated the protein base from which pathogenic organisms operate without giving rise to new toxic products, that it destroyed toxins already produced by pathogenic organisms, and that it did not attack living tissue. He obviously recognized the importance of removing devitalized and infected tissue from wounds. He considered his method for cleansing wounds with a bacterial agent superior to surgical débridement because it was microscopic rather than macroscopic.

Further animal experiments showed that the organisms did not survive when injected intraperitoneally in mice. Donaldson also found that mice could survive 148 M.L.D. of tetanus toxin and that guinea pigs withstood 60 M.L.D. of diphtheria toxin "neutralized" by the action of the "Reading" bacillus. He and Joyce were successful in their attempts to prove that inoculation of wounds with the "Reading" bacillus and packing them with sterilized bags of sphagnum moss was just as effective as packing them with salt bags. They therefore concluded that salt was not necessary for the effects but that packing was needed to create the anaerobic conditions essential for growth of the bacteria. The sphagnum moss actually appeared superior to the salt bags because as it became moist it expanded to fill each crevice of the wound and it did not cause the pain associated with the irritation of salt. Thus, some of the theories of Wright regarding the "lymphagogue" action and other benefits claimed for hypertonic saline were shaken at their very foundations.[6]

Although Donaldson strongly advocated that his colleagues try his method and generously offered to supply them with cultures of the "Reading" bacillus, few seem to have shared his enthusiasm. He recognized that he was being criticized by some of his colleagues for this work and showed remarkable insight by acknowledging that the deliberate contamination of a wound with a bacterium, and a spore-forming anaerobe at that, was an idea almost certain to generate universal horror among surgeons. The almost unanimous reluctance of surgeons to accept or even try the unorthodox procedures advocated by Donaldson appears to have caused the matter to be dropped and forgotten after World War I when gunshot wounds ceased to be a problem of major concern. So far as can be determined, the exact procedure of Donaldson never was revived, and the "Reading" bacillus appears to have been lost to posterity.

What was the "Reading" bacillus? Donaldson explained that he named it after the Reading War Hospital in which it was isolated. He expressed his content with leaving the nomenclature at that at the moment, not only because of the greater urgency of other matters, but also because of his dissatisfaction with the nomenclature for anaerobes at that time. Although he performed rather complete studies of the cultural characteristics of the "Reading" bacillus, the closest Donaldson seems to have come to classifying it appears in his statements that it belonged to the same group as *B. oedematis maligni* and *B. tetanus.* Of the numerous organisms he investigated, the "Reading" bacillus and, to a lesser extent, *B. sporogens* (Metchnikoff) were the only ones he found capable of destroying tetanus toxin. Another similarity between the "Reading" bacillus and *Bacillus sporogenes* was the property of forming black precipitates in the bottoms of certain cultures.

The "Reading" bacillus appears to have resembled somewhat the "Bacillus X" of Fleming.[7] Donaldson also noted some similarities between the "Reading" bacillus and the one isolated by Miss Robertson,[9] but he stated that he did not feel disposed to follow Miss Robertson's lead regarding nomenclature for his organism. His indisposition seems well grounded, for Robertson described the organism which she isolated (called "Hibler IX," after von Hibler,[11]) as a nonliquifier of gelatin incapable of attacking proteins. Her bacterium also seems to have been pathogenic, at least in symbiosis with other organisms, and it formed no black precipitate in cultures. Several modern scientists[1, 8] seem to believe that the "Reading" bacillus was actually a form or a strain of *Clostridium sporogenes.*

Donaldson was an all-round pathologist. He was qualified in tropical medicine and public health and was readily interested in almost any pathologic subject. He was most active at Reading during the war, working at the meningococcus, typhoid, sporing anaerobes, influenza, and so forth. Donaldson was born at Dalkeith in 1877 and educated at the Royal High School and the University of Edinburgh. He died unexpectedly of pneumonia on Jan. 3, 1933.[8] His work with the "Reading" bacillus formed the basis for his thesis for the degree of Doctor of Medicine, which he was awarded with commendation by the University of Edinburgh.

Although Donaldson's method for treating war wounds seems to have passed into oblivion along with the "Reading" bacillus, his work emphasized the point that bacteria can be turned to therapeutic use. Specifically, Donaldson pointed out the proteolytic and the detoxifying capabilities of the "Reading" bacillus. In view of the discovery and development of antibiotics derived from bacterial sources, one can scarcely refrain from wondering whether the "Reading" bacillus may also have produced antibiotics which would have enhanced the other benefits derived from this organism. If the "Reading" bacillus were indeed *Clostridium sporogenes,* the probability of antibiotic production by this organism is remote because none of the Clostridia is listed among the numerous micro-organisms which produce the 340 antibiotics described in a recent standard reference.[10] If the "Reading" bacillus was not *Clostridium sporogenes,* the probability that it was producing antibiotics in addition to "proteoclastic ferments" may be somewhat more likely, and Donaldson may have missed his chance to precede Fleming and Florey in the discovery of antibiotics.

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Harvey Cushing: surgeon and teacher

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I presume that one of the functions of any society of history, medical or other, is to hold before us mortals as a group the mirror of introspection so that, by seeing ourselves in that mirror in proportion to the truly great figures of whom we read, we of succeeding generations raise our own ideals and strengthen our own resolves. The instinct of self-comparison is deeply ingrained in us and is, I suppose, the wellspring of the strength of what we of the West call the individual enterprise system. From this instinct of self-comparison, sufficiently widespread and possessed of proper standards, a particular civilization may derive great impetus. Sir Richard Livingstone,[3] in his essay *Character and Its Training,* cites Professor Whitehead's statement, "Moral education is impossible without the habitual vision of greatness." Livingstone goes on to say, "Outside Plato there is no profounder saying about education. A 'habitual vision of greatness' is necessary not only to moral education but to all education." The subject of this paper, Harvey Cushing, can justifiably be said to present such a vision and if, as we proceed, we note occasional overtones of human frailty, perhaps they will serve the purpose of reminding us "shallower vessels" that even the great have faults and by that very fact become to us more understandable.

Something of the man's character may, I think, be gathered from 2 photographs (Figs. 1 and 2). In the first he is shown as the thoughtful surgeon surveying a clinical problem, and in the second as the general physician.

But the crayon portrait of Deane Keller (Fig. 3), made somewhat later, catches a harder and sterner Cushing, square-jawed, intense, severe—the man remembered by some of his junior assistants as uncompromising and dictatorial and a leader of indomitable purpose.

The recognition of his ultimate stature is documented by the assessment of Dr. William H. Welch, the first and most important appointee (1884) to the medical school faculty of Johns Hopkins University. Upon returning from the First International Neurological Congress, held at Berne in 1931, Dr. Welch told Dr. Samuel Crowe of the Hopkins staff, "Cushing was given a great ovation, and is undoubtedly the outstanding medical figure in the world."

To place Cushing properly in relation to neurological surgery, general surgery, and to medical education, one must look back to the nineteenth century. There is perhaps no better way of condensing this period than by referring to a paper of John Collins Warren (1842-1927), one of the succession of a distinguished Boston surgical family.

It seems worth while to make a record of some of my personal recollections because I have been so situated as to be more or less intimately in contact with the prime movers in that great change which was brought about in surgery by the introduction of anesthesia. Although I was only four years of age at the time of this historic event, my relations to many of the parties concerned were such that I have always felt that I had more or less personal knowledge of an epoch in medicine and surgery which marked the beginning of a new and great era.

Surgery had made but few advances during that

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portion of the nineteenth century which preceded the public demonstration of anesthesia at the Massachusetts General Hospital on October 16th, 1846. The wars of the early part of the century had no doubt improved greatly the technique of surgical operations which the master minds of Baron Larrey in France, Sir Astley Cooper in England, and others had done so much to design. The operation of lithotrity introduced by Jean Civiale was beginning to displace the time-honored cutting for stone, but it stood out as rather a brilliant exception to what was otherwise a persistence of old methods.

Surgery was responding, of course, to the stimulus given by a more intimate knowledge of anatomy and pathology, but innovations even at the great medical centers were few and far between. Surgical operations in civil practice were rarely operations of choice, for it was only dire necessity that forced a patient to submit to the knife. The number of operations performed was extremely small, except in war time. The surgical service at a hospital could not absorb a great deal of the surgeon's time, and there were few men indeed who undertook to limit their practice to surgery alone, as can be seen by a study of the lives of the prominent physicians of that period. The number of operations was so small that when an opportunity to demonstrate the advantages of sulphuric ether as an anesthetic agent was sought by Dr. Morton at the Massachusetts General Hospital, it was necessary to wait a fortnight before a suitable patient turned up.

The historic event of the discovery of anesthesia marks the close of the first of three great eras. The second era, from Morton to Lister, was distinguished by only a moderate increase in the scope of surgery. During this period, owing to the abolition of pain, operations increased tenfold in number, although there were no corresponding improvements either in the technique of the operations or in the management of wounds. Surgeons were equipped neither by skill nor by scientific knowledge to keep pace with the changes ushered in by the great discovery. So the second era, during which my medical career began, was replete with the dangers and complications which inevitably arose from the crowding together of numbers of surgical patients. Civil surgery came to have as high a mortality as that which marked the campaigns of the Napoleonic wars. It was not until two decades after the introduction of anesthesia that the pioneer work of Louis Pasteur paved the way for Joseph Lister's first studies on the causes of wound infection. This made it possible to contend with hospital infection, at first by means of chemical disinfectants. The second era may fairly be said to have covered three decades, for it was not until after another ten years that antiseptic surgery began to be replaced by aseptic surgery and anything like the modern standard of operation room techniques and care of wounds was approached.

The third era, or the modern one in which the present generation rejoices, was eventually established on a firm basis. It is safe to say that no other generation of physicians in the history of medicine has seen such extraordinary changes in the practice of medicine and surgery as have been witnessed by the generation of which I have been a member.[1]

For the development of neurological surgery as a specialty, however, another discovery was essential. This occurred in 1870 and was the demonstration by Fritsch and Hitzig of the electrical excitability of the

Fig. 1. Dr. Cushing viewing an x-ray film in his dressing room after an operation. (From J. F. Fulton.[2])

Fig. 2. Photograph of Dr. Cushing with a child a few days after removal of cerebral tumor. (From J. F. Fulton.[2])

Fig. 3. The crayon portrait by Mr. Deane Keller from *Harvey Cushing's Seventieth Birthday Party,* published for the Harvey Cushing Society by Charles C Thomas, Publisher, Springfield, 1939.

cortex of the dog. This opened up a wholly new field of physiologic investigation, which was developed chiefly in Great Britain by a distinguished group of investigators whose studies culminated in the nineties in the exploration of the anthropoid brain by Sherrington and his collaborators. Fortunately, among the group of early workers was a general surgeon trained at the University College, London—Victor Horsley by name (1857-1916). The experience gained in exposing the brain, in meeting the special problems of hemorrhage, and in dealing with cerebral tissue prepared Horsley for his appointment at the age of 27 to the staff of the National Hospital, known affectionately to neurologists as "Queen Square," London. To Horsley, more than to any other single person, can properly be applied the term "father of neurological surgery." It was Horsley, a man of great courage, intensity, and drive, trained as physiologist as well as surgeon, who pioneered the specialty, who introduced the curved scalp flap which respected vascular supply, who developed bone wax to control bleeding, who was one of the first to remove a brain tumor, and who was the first to remove a spinal cord tumor (in 1887).

This, then, is the backdrop of the stage onto which Cushing moved. He was born in 1869, the fourth of a line of physicians. He had a usual sort of favored childhood in a Cleveland professional family and went to Yale for his college work. There he distinguished himself more in baseball than scholarship, and admitted having entered the library only once during his collegiate career. In 1891 he went on to the Harvard Medical School.

Apparently while in medical school he suffered the same feelings of inadequacy that plague all good, conscientious students, but his scholastic record was excellent there. He was awarded the degrees of M.D. and A.M., *cum laude,* in 1895.

An event of undoubted importance occurred well along in his second year of medical school. While anesthetizing a patient before the class at the Massachusetts General Hospital, he lost his patient. This had a profound effect upon Cushing and caused him for a time to consider leaving medical school. Eventually, however, a more rational reaction occurred and this led him with his friend, Amory Codman, to devise the basic form of the ether chart which we all use today with no thought of the circumstances which led to its development.* One can only speculate on how profound an influence the incident may have had on the development of Cushing's high standard of patient care, which all who knew him readily acknowledge.

After graduation, Cushing was given an appointment as a House Officer at the Massachusetts General Hospital. But already he was not an easy colleague with whom to work, as is indicated by the following quotation from Fulton.[2]

> H. C.'s contemporary comments on M. G. H. surgery are few, but they are pungent. The work

*Dr. Codman's account of the genesis of the ether chart differs substantially from that of Dr. Cushing and denies credit to both Dr. Codman and Dr. Cushing for the original idea. (Beecher, H. K.: Surg. Gynec. & Obst. 71: 689, 1940.)

of John W. Elliot, C. B. Porter, Maurice Richardson, and William Conant he held in high esteem, but some of the others operated by the clock. For example, on 12 April 1896, he writes: "Not operating much. Considerable sepsis in the house. No wonder, these men operate about the way a commercial traveller grabs breakfast at a lunch counter."

A man of H. C.'s driving energy could not live long without arousing animosities among those with whom he was thrown. He was a severe taskmaster, demanding of others a standard of performance similar to that to which he himself aspired. Franklin S. Newell who served under him at the M. G. H. and who later came to occupy the chair of Obstetrics at the Harvard Medical School writes on 6 April 1942: "He was recognized as perhaps the ablest man in his class at the Medical School and was an extremely hard worker. As house officer I was his junior and suffered severely in that position for a year. He was an extremely hard man to work with, whether one was over him or under him, as his tremendous ambition for success made it impossible for him to allow anyone else to get any credit for work done. As you know, when he wanted to be he was one of the most charming people in the world, but working with him I found that he couldn't tolerate anyone else in the limelight."

From the Massachusetts General Hospital Cushing went on to the newly established surgical service at the Hopkins, which, with great wisdom, William H. Welch had chosen William Stewart Halsted to direct. The genius of Welch's choice was additionally validated by the fact that Welch knew that while Halsted had been working with a wholly unknown drug, cocaine, in the effort to develop an anesthetic agent, he had become addicted to it. Such was Welch's belief in the integrity and promise of Halsted that he none the less arranged for his appointment at the Hopkins and supported him throughout his personal Gethsemane to ultimate triumph over the addiction.

Cushing, accustomed to the hurly-burly of the Massachusetts General Hospital, to the operating-by-the-clock that characterized much of the surgery of that day, and to the rapid turnover of patients, found both the Hopkins and "the Professor" difficult to accept. But before long he settled into the swing of things, and after Halsted's death in 1922 Cushing gave ample evidence of his deep gratitude to the training Halsted made available to him, as is clear in the following appreciation:

> . . . A man of unique personality, shy, something of a recluse, fastidious in his tastes and in his friendships, an aristocrat in his breeding, scholarly in his habits, the victim for many years of indifferent health, he nevertheless was one of the few American surgeons who may be considered to have established a school of surgery comparable, in a sense, to the school of Billroth in Vienna.
>
> He had few of the qualities supposed to accompany what the world regards as a successful surgeon. Overmodest about his work, indifferent to matters of priority, caring little for the gregarious gatherings of medical men, unassuming, having little interest in private practice, he spent his medical life avoiding patients—even students, when this was possible—and, when health permitted, working in clinic and laboratory at the solution of a succession of problems which aroused his interest. He had that rare form of imagination which sees problems, and the technical ability combined with persistence which enabled him to attack them with promise of a successful issue. Many of his contributions, not only to his craft but to the science of medicine in general, were fundamental in character and of enduring importance. . . . [2]

Cushing spent 4 years on the surgical service at the Hopkins in his initial period there and advanced by successive steps. But perhaps of equal importance to the Halsted association was the opportunity to be influenced by "Popsy" Welch, that great figure of American medicine, and by William Osler.

At the turn of the century, study on the Continent was still a regular aspiration of men who sought the best in medical training. Cushing went to London in 1900, expecting to work with Horsley, but he found Horsley too absorbed in private practice and in the social problems that had come to intrigue him—woman's suffrage, temperance, and the political affairs of the British Medical Association.

Accordingly, he went on to Berne, for he had earlier expressed an interest in working under Kocher. Here, after waiting for some 3 weeks, he was assigned a problem by

Kocher, which was worked out in the laboratory of Kronecker, the physiologist. This was the famous set of experiments concerned with the increasing blood pressure and the slowing pulse that Cushing found to accompany the artificial production of increased intracranial pressure consequent to the continued addition of fluid into the cisterna magna.

His many months in Berne were followed by a visit to Italy, and finally he spent the month of July, 1901, working in Sherrington's laboratories at Liverpool (Sherrington not yet having gone to Oxford). He performed craniotomies on anthropoids. The story goes that as a gorilla was operated upon there were 4 on the team, Sherrington, Cushing, the anesthetist, and a diener with a high-powered rifle—should the anesthesia prove imperfect.

Cushing returned to the Hopkins on a vague and indefinite assignment from Halsted. The latter recommended that he take up orthopedic surgery, a newly developing field, since there were only very occasional neurosurgical cases amenable to surgical treatment. Cushing, however, with his usual tenacity, persisted in his objective and despite appalling initial mortality rates, struggled on. His Baltimore years, extending to 1912, were full of activity—operations for brain tumor came with increasing frequency, he developed better methods for approaching the Gasserian ganglion in cases of trigeminal neuralgia, he evacuated intracerebral hemorrhages, and he developed techniques for improving hemostasis. In 1908, stimulated by a visit from the English physiologist, Edward Shafer, he became interested in the hypophysis and by 1912 he had gathered 50 well-documented cases in a book entitled *The Pituitary Body and Its Disorders.* There were many other papers, and he was frequently asked to talk on the new subject of neurological surgery at various state medical society meetings. Stimulated by Welch and by Osler, he began to develop the tastes of a bibliophile. Several invitations to accept chairs of surgery were received during the Baltimore period. The later ones were rejected because he had been given some reason to believe that he might be called back to Harvard.

Meantime he was developing temperament also. Fortunately "W. O." was there to exercise a restraining hand. Thus, in a handwritten note dated March 3, 1902, the following was said:

> Dear Cushing
> I arranged with Dr. Hurd—he did not understand that they were your private patients. He must have you put on the Hospital Staff in some way officially.
> You will not mind a reference to one point. The statement is current that you do not get on well with your surgical subordinates & colleagues. I heard of it last year & it was referred to by a strong admirer of yours in N. Y. The statement also is made that you have criticized before the students—the modes of dressings, operations &c of members of the staff. This, I need scarcely say would be absolutely fatal to your success here. The arrangement of the Hospital staff is so peculiar that loyalty to each other, even in the minutest particulars, is an essential. I know you will not mind this from me as I have your interests at heart. Sincerely yours, Wm. Osler.[2]

This note was later followed by another which is undated but seems to have been in relation to the response to the former letter.

> Dear C.
> Do nothing of the kind! Who is free from faults—and failings! It is a simple matter—"Keep your mouth (as the Psalmist says) as it were with a bridle." Your prospects here are A1 & we need you. Yours ever, W. O.[2]

In 1905, with an initial sum of $15,000, Cushing and MacCallum established the Hunterian Laboratory, named for John Hunter. To this laboratory in 1910 came a brilliant young man, so like Cushing in many ways that there was bound to be conflict. This was Walter Dandy who, when Cushing left for Boston in 1912, succeeded him and made tremendous contributions to the specialty, the most notable being that of pneumoencephalography, a boon of inestimable value to patients and surgeons. Cushing's long-delayed acceptance of this important diagnostic maneuver must be charged to his antipathy toward Dandy.

Cushing's own research was of an intuitive character and once he settled upon an idea the objective of the investigation he carried out was to prove the correctness of his hypothesis. Conrad Jacobson, who became his Hunterian Fellow the year after Dandy's term of service in the laboratory, had this to say later of Cushing's methods:

> As a research man he was of the deductive type of mind. Some investigators gather their data and try to draw their conclusions from them. He was inclined to have a theory and then use all of his efforts and ingenuity to prove the validity of it.
>
> Cushing's interpretation of certain facts which were produced experimentally under his direction undoubtedly has been rather too enthusiastic and had been and will be questioned. When he was reminded of these facts by some of his contemporaries, he usually remarked, "I never expected to settle these things; I have set others thinking about them and this is the main purpose, after all." He had the most remarkable power of writing a paper. Quotations from the recesses of the literature as well as experimental facts were used to prove his contention. His papers were all frankly readable. One feels that Cushing's greatness in the research line is due more to his interpretation of clinical findings from his operative cases than to the experimental work on animals.[2]

In 1910 Cushing accepted the anticipated call to Harvard and with Henry Christian in medicine and W. T. Councilman in pathology, the new teaching service was established at the Peter Bent Brigham Hospital in 1912. The set of buildings was not actually completed by the time of Cushing's arrival, and this was a source of some early friction between him and the president of the Brigham Board. He and Christian worked out a practical and workable program for the administration of the hospital. Among the rules on which Harvey Cushing insisted was that of retirement at the age of 63, a ruling which he later found difficult to accept.

The war years took him away from Boston for 2 periods, the first with the British Army, the second with our own American Expeditionary Force. Though once very nearly court-martialed for the keeping of a diary and for certain other nonconformist attitudes toward military discipline, he somewhat belatedly in 1926 received the Distinguished Service Medal for his wartime contributions to military surgery. *From a Surgeon's Journal,* published in 1936, is a most readable account of his wartime experiences.

Returning to the United States after the close of the war and focusing his attention on the development of a concerted attack on brain tumors, he soon established a school which in the last 15 years of his Boston life attracted men from all over the world, men who in time influenced profoundly the further development of neurological surgery.

There were generally about 40 patients on the clinical service, sometimes more. But the turnover was slow, for Cushing usually operated upon only 1 patient a day, sometimes 5 and sometimes 6 days in a week. Openings and closings might be carried out by his assistants, but it was he himself who carried the load. Seldom, except at time of holidays or trips, did he share the operating with his juniors.

But his interests were not limited to the clinic alone. He had established at Harvard an Experimental Surgery Laboratory similar to the Hunterian at the Hopkins. As was the case at the Hunterian, a series of young surgical residents took charge of the laboratory and were responsible for the teaching of dog surgery to the students. In October, 1920, Percival Bailey, on a second tour of duty with "the chief," was appointed Arthur Tracy Cabot Fellow, an experience which made up a part of 7 years spent with Cushing at various times. Bailey gives an enlightening account* of the preparation of the famous monograph, *Classification of the Gliomas,* which he published jointly with Cushing:

> When I came back to Boston in the summer of 1922, Dr. Cushing asked me to create a histological laboratory for the study of his collection of brain tumors in which he had tried for years, without avail, to interest the pathologists. Now he had obtained some money from the heirs of one of his patients, Mr. Philip Gray, and with this I set to work, not feverishly as John Fulton would have it, but industriously and stubbornly

*Unpublished material.

since this group of tumors was quite variegated and the attempt to bring order into it did not succeed easily. I was also to have the operating to do on one public ward, Paul Martin on the other, and, in November, McKenzie came on as resident. In his obituary of Dr. Cushing, McKenzie gives what purports to be a typical day's schedule from this period. Among other things he says that Dr. Cushing spent an hour daily with me going over the tumors. This is not true. In all the months during which I struggled with this problem Dr. Cushing never spent even one hour altogether in the laboratory. He would have been only a nuisance if he had since he knew nothing of cytology. I continued to work at the task alone with occasional relief by examining patients and operating.

We were now both deeply engrossed, he with his biography of Osler, I with my gliomas. So we did not clash again until the spring of 1925. Just before Christmas 1924 I had called him into the laboratory and shown him my solution of the glioma problem. He was very enthusiastic and said we must publish it right away. I protested that I had made only a tentative formulation and must do more work. The matter was dropped over the holidays but then he returned to the charge since he had agreed to give the Cameron Lectures in Edinburgh and wished to deal in one of them with the gliomas. He demanded the list of gliomas with their diagnosis and I was obliged to comply but was deeply annoyed by his dictatorial attitude. So I applied for and received a Guggenheim Fellowship, the first to be given, and announced that I was sailing for France in July. Before leaving I prepared lantern slides for his Cameron Lecture but did not label them. He discovered this as I was leaving and I had to sit down and write a description of each one at the last minute, nearly missing my boat as a result. Thus it came about that he wrote the last chapter of the monograph on the Glioma Group himself and saw the book through the press after my departure.

There followed a later monograph (1928), again with Percival Bailey, *Tumors Arising from Blood-Vessels, Intracranial Tumors* (1932), which surveyed the results in a series of 2,000 patients with verified tumors, *The Pituitary Body and Hypothalamus* (also 1932), and the great classic *Meningiomas* (1938), with Louise Eisenhardt. Cushing's *Life of Sir William Osler* (1925), for which he won a Pulitzer prize, is a must in any medical student's orientation in the development of modern medicine in Great Britain and on the North American continent.

Reference was made in the account of the Baltimore period to the fact that Cushing was a forceful character. This was evident also during his Boston days and the following quotation is taken from Edward Churchill's editing of the Warren papers,[1] quoted at some length because it indicates a difference between the line of administrative development in Boston and that in Baltimore.

On April 11, 1898 it was noted by the Harvard Corporation "that the bequest of William Oxnard Moseley be appropriated to the endowment of a professorship of surgery in the Medical School to be hereafter known as the Moseley Professorship of Surgery." On June 28, 1899 Dr. Warren, whose professorship dated from May 29, 1893, was designated Moseley Professor of Surgery. On his retirement in 1907 Maurice H. Richardson was elected to this named chair in his place.

Subsequent events pertaining to the Moseley professorship will be mentioned briefly at this point. They reveal Dr. Warren's concept of the department of surgery at the Harvard Medical School, and also point up the differences between his concept—one which prevailed in American universities up to that time—and a new pattern of academic organization derived from the Continent of Europe. The pressure for change to this new pattern was a by-product of the developments that followed the building of the new school in 1906.

After Dr. Maurice Richardson's death in 1912, which came at the end of a busy operating day at the MGH, the Moseley professorship went to Harvey Cushing, who had accepted an invitation to take up the duties of surgeon-in-chief at the new Peter Bent Brigham Hospital. Dr. Cushing received his medical degree from Harvard in 1895 and served a year as house pupil on the old South Surgical Service at the MGH. Transplanted to Baltimore, he soon began to flourish in the heady atmosphere of the new Johns Hopkins Hospital. Osler, in referring to the organization of this hospital, once said: "For the first time in an English-speaking country a hospital was organized in units, each one in charge of a head or chief." This statement would have been modified had Osler recalled that in 1821 John C. Warren and James Jackson took the position that each professional service at the MGH should be headed by a chief with continuous service. Actually, such an organization was maintained until 1835. . . . But irrespective of this omission, Osler was correct in emphasizing the fact that the continental type of clinic structure introduced in Baltimore was new to the American medicine of that period. The form—a hospital teaching service with a professor

at the apex—was customary in the university centers of German-speaking countries. This structure was adopted wholeheartedly at the Hopkins as preferable to the older institutional patterns, originally derived from England and Scotland and still prevailing in one form or another in Philadelphia, New York, and Boston. The essential feature of the old pattern was distribution of the responsibility for ward patients among a number of practitioners, each of whom conducted a "service" during from two to six months a year as a side line to his private practice in the community.

The German conception of a university, which strongly influenced The Johns Hopkins University and was projected into the organization of the Johns Hopkins Hospital, placed greater weight on the extension of knowledge through research than on the transmission of knowledge by instruction. This conception was almost twice removed from that of such beloved institutions as the Pennsylvania Hospital, the New York Hospital, and the Massachusetts General Hospital, all patterned after British voluntary hospitals and supported by a philanthropy which directed them in their Good Samaritan missions. Cushing had ample opportunity to become familiar with the Continental type of department in his travels, and during his stay in Berne worked close to the surgical department organized in the German manner under Theodor Kocher.

It is not surprising, therefore, to find that Dr. Cushing, in his negotiations with President Lowell before accepting the Harvard invitation, pressed for recognition as "head of the surgical department" in the Medical School instead of being satisfied with one of several professorships of surgery. Lowell remained non-committal on this point, however, and in a terse sentence informed Cushing that the professorship Harvard was offering him "would be a professorship of surgery, and would involve surgical teaching in the Medical School." The fact that other great hospitals had been partners in the teaching of Harvard medical students, long before the Brigham, made the Boston situation quite different from that at the Hopkins.

At an earlier date (1907), when Cushing had taken the opportunity provided by an offer from Yale to feel out the Harvard situation, Dr. James G. Mumford had written:

"Dear Harvey: Here's a confidential word regarding plans: It must have been evident to you that your friends here, Dr. Warren, Allie Porter (Charles Allen Porter, son of Dr. Warren's contemporary, Charles Burnham Porter) and your humble servant, have long been striving to bring about an arrangement by which you might be called to a Chair of Surgery at Harvard. . . . Allie and I have worked out a rather simple plan, which is now being considered by the authorities, but before pressing it further I am writing to you without other authority than my own, to ask your opinion of it. Essentially, it is this:

"That on Dr. Warren's present retirement, there be continued the three professors, Bradford, Richardson and Burrell, and that you be added—making four; that the 4 hold equal rank; that they choose from among themselves a Chairman or Dean; that Richardson continue in charge of the M. G. H. teaching and Burrell of B. C. H. (Boston City Hospital); that the four reorganize the general teaching scheme—especially the didactic work, laboratory work, animal work, neurological surgery, etc., with reference to your interests; that pending the erection of the Brigham, in which you should have a hand, the Brigham people might open a surgical dispensary somewhere; and that you be given beds at the M. G. H. until your own hospital is completed. (As quoted in John F. Fulton, "Harvey Cushing: A Biography" Thomas, Springfield, Ill., 1946, p. 336)."

But such egalitarian ideals did not satisfy Harvey Cushing. After receiving Mr. Lowell's letter with its definition of the post being offered, he drafted a letter pressing the point by a direct question but on second thought decided not to drop it in the mail. He did, however, express to the president a desire that in due time he be given the title of Moseley professor. The letter in which this was done (not included in the Fulton biography) was not well received in Boston, where it was read by Dr. Maurice Richardson among others. Apparently it carried the suggestion that Dr. Richardson might be ready to hand over the Moseley title in about two years. At any rate, Dr. Warren's pupil and assistant, Dr. Robert B. Greenough, thought it timely to warn Cushing that he was treading on sensitive and important toes. As events happened, Maurice Richardson died on the last day of July, 1912; Cushing's election as Moseley professor was confirmed as from the first of September, and shortly thereafter he returned to Boston to take up the surgical portfolio at the Brigham.

President Lowell was fond of saying that power in this world is never conferred, it is always seized. The Moseley professorship soon became known as the senior chair of surgery, although it had been in existence only fourteen years; it also became identified in the minds of many as synonymous with the position of head of the surgical department at Harvard, which did not exist. The vision cherished by Warren, Porter, and Mumford of a federation in which decisions were to rest on the common sense of most after the consultation of all, faded away. Before long, by some ingenious extrapolation, the academic lineage of the third Moseley professor was projected back beyond Maurice Richardson and J. Collins War-

ren, through Henry J. Bigelow, George Hayward, and John C. Warren (a founder of the MGH) to the first John Warren, Hersey Professor of Anatomy and Surgery. When Dr. Cushing retired, President Lowell and Dean Edsall made it clear that the large clinical departments are made up of separate budgetary units corresponding to the major teaching hospital services and that professors in a department are of equal rank.

Prior to his retirement there had been hope on his part that he might be allowed to remain at the Brigham, utilizing his clinical records. Elliott Cutler, pupil, friend, and Cushing's own choice for the succession, found it expedient to deny this to Cushing. Even the soft words of John Fulton[2] hardly conceal the disappointment Cushing felt:

> For the first time (in October, 1932) Cushing returned from Europe without having to face clinical responsibilities. Cutler, knowing that he wished to be relieved completely of patients, had arranged a place for him in the surgical laboratory where he would be at liberty to consult his case records, but where he would no longer assume any part in the direction of the clinic. Cutler had begun at once to rearrange the offices which he had inherited from Cushing and to alter the routine of the operating room. Psychologically, the return to the clinic which he had once directed was naturally upsetting, and while he kept his peace with Cutler, he seemed unconsciously disappointed that he had been so completely superseded. Since Cutler knew Cushing's temperament, he acted in the belief that complete abrogation of Cushing's responsibilities was essential—not only in theory but in fact. Without question this wounded H. C. immeasurably, for he had no doubt hoped that even in retirement he would be consulted not only by Cutler, but by his junior staff. The hurt was perhaps somewhat ameliorated by an appreciative vote of the Brigham Trustees appointing him Surgeon-in-Chief Emeritus. . . .

The decision had been made in June of 1932 to return to New Haven where facilities were made available to him to carry on some clinical work and a year later a Brain Tumor Registry was established in New Haven with Louise Eisenhardt in charge. By the fall of 1933 Cushing had concluded his Boston affairs and he and Mrs. Cushing took up residence in New Haven where Cushing had been appointed the Sterling Professor of Neurology.

In the succeeding years he was plagued with poor health. His great contributions of this period were the setting in order of his library and of his papers, and the evolution of a plan whereby his own library was to be joined with those of his friend and biographer-to-be, John Fulton, and Arnold Klebs, the Swiss bibliophile and Cushing's European companion of many a transatlantic visit. In December, 1937, he became Emeritus Professor. On April 8, 1939, The Harvey Cushing Society honored him on his seventieth birthday by meeting with him in New Haven. In June, 1939, to his great joy he was elected to Honorary Fellowship in the Royal College of Physicians. A month later the university announced that $600,000 had been appropriated for a new medical library, one wing of which was to be devoted to the newly proposed medical historical library, a fitting culmination to his years of interest in medical history.

On October 7, 1939, death came to Harvey Williams Cushing, surgeon and teacher, a great man and a great intellect, fallible, strong-willed in both the good and bad connotations of the term, always challenged by the continuing intrigue of clinical problems, proud and dominated by a sense of his place in history, fragile at times, and yet a man to whom all of us in medicine today, directly or indirectly, stand in debt. From his life we may learn of some mistakes to avoid. Could we emulate his intensity of purpose and his devotion to the sick, the medicine of our generation would be the richer.

APOLOGIA

Some of my auditors, after hearing this paper read, urged that it be prepared for publication. I have been reluctant to do so, knowing that there are many who knew Dr. Cushing far better than I knew him. The manuscript has therefore remained on my desk for many months. With some further urging, however, I have revised the paper, believing that such value as it may have, particularly for medical students, lies in its description of an era as much as in its limited portrayal of a man.

My indebtedness will be evident to 2 people in particular and is hereby gratefully acknowledged. One is the late John Fulton, from whose biography

of Dr. Cushing I have drawn so freely. The other is Percival Bailey, whose narrations of his associations with his master I have been privileged to hear on occasions from 1930, when, as a surgical intern in Chicago, I occasionally assisted him at the operating table and heard him reminisce during craniotomy closures, down through the years until his richly appreciative presentation before the Society of Neurological Surgeons in late April of 1960. My small account will detract in no way from his eventual presentation.

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The surgical achievements of ancient India: Sushruta

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A surgeon making a wrong operation on the body of his patient either through mistake, or through the want of necessary skill or knowledge, or out of greed, fear, nervousness or haste, or in consequence of being spurned or abused, should be condemned as the direct cause of many new and unforeseen maladies.

Sushruta

Presently, India has at least 40 medical colleges, some of which are connected with universities. Others function independently, following the example of the British hospital schools, but in all of them modern Western medicine is taught and the graduates compare favorably with those trained in the West. It is clear, however, that these 40 medical schools cannot possibly supply a sufficient number of physicians to care for the entire population of India, which exceeds 392 million. Because of this dearth of Western-trained doctors, practitioners of the ancient Ayurvedic art of healing have continued to flourish in large numbers, and indeed they are actually preferred by many Indian patients, partly because of their faith in tradition and partly because the awakening nationalism in India puts increasing stress on the Indian cultural heritage. Ayurveda, the Science of Longevity or of Life, is an integral part of India's ancient culture and it was doubtless one of the best-developed medical systems of antiquity, comparable to that of the ancient Greeks. Indeed, some parallels and similarities between Indian and Greek medicine are so striking that they have given rise to unending speculations concerning cross-cultural influences. However, the special subject at hand, the surgical art of India, is doubtless *sui generis* and does not bear any traceable resemblance to the contemporary surgical practices of any other culture.

According to Zimmer,[8] Ayurveda, as it originally evolved among the Brahman doctors, was not concerned with surgery. The latter branch of medical science became an accepted part of Hindu medicine only in the first century A.D., but it is undoubtedly of much greater age. The name for surgery was "alya," or "arrow," after the most important weapon used in the Hindu warfare of the Vedic period and the subsequent centuries, for as in all other cultures, surgery advanced through the care of wounds sustained in battle. Because of this origin, however, it remained a special branch of medicine apart from the general Science of Life, which was in the custody of Brahman physicians. Even though border warfare between the first Aryan settlers in the Punjab and the dark aborigines of the country made the surgeons' ministrations indispensable to the Aryan warriors, surgeons were rarely allowed to enter the Brahmanic Society of Vedic India. The bridging of the social gulf between the war-born surgeons and the civilian Brahman physicians was accomplished by the work of one personality, Sushruta, whose encyclopedic writings made surgery a vital part of the general art of healing. His collective works, the *Sushruta Samhita,* not only comprised a textbook of surgery, but also systematized

and clarified much of the earlier general medical thought as it had been recorded by Charaka, and served as a basis in form and content for subsequent medical authors.

Neither Indian nor Western scholars have as yet succeeded in the accurate dating of any of the Indian medical classics. It is uncertain whether Charaka, the compiler of Ayurvedic medicine, and Sushruta, the author of the surgical text, were actual historical personages or simply legendary figures to whose authorship these collective works were attributed. Sushruta's life has been placed in periods varying from the sixth century B.C. to the sixth century A.D. It is only certain that the *Sushruta Samhita* was written well before the eighth century A.D., for it then served as a model for another classical medical author, Vagbhata. In view of the uncertainty as to the dating of the work and its author, the Indian traditions which make the greater claim concerning Sushruta must suffice, although in evaluating these beliefs the Oriental tendency of equating venerability with great age must be borne in mind. Thus we read in the most authoritative English translation and edition of his work that Sushruta was a disciple of the holy Dhanvantari, the first proponent of medical science, and that his style of writing proves him a contemporary of Buddha (circa 600 B.C.). It is further stated that "Sushruta was emphatically a surgeon, and the *Sushruta Samhita* is the only complete book we have which deals with the problems of practical surgery and midwifery. . . . To Sushruta may be attributed the glory of elevating the art of handling a lancet or forceps to the status of a practical science. . . ."[1]

With the *Sushruta Samhita* the development of Indian surgery reached its acme and its end. Little, if anything, other than commentaries upon this text, was added in the subsequent centuries. Thus, in studying this one work we also analyze the totality of Indian surgery and, incidentally, the highest achievement of Indian medicine, for in this book surgery is considered the foremost branch of the entire healing art and appears as the first of the 8 branches of Ayurveda. It is defined in the opening chapter of the *Sushruta Samhita* as:

> 1. Surgery—The scope of this branch of Medical Science is to remove (from an ulcer) any extraneous substance such as fragments of hay, particles of stone, dust, iron or bone; splinters, nails, hair, clotted blood, or condensed pus (as the case may be), or to draw out of the uterus a dead foetus, or to bring about safe parturitions in cases of false presentation, and to deal with the principle and mode of using and handling surgical instruments in general, and with the application of fire (cautery) and alkaline (caustic) substances, together with the diagnosis and treatment of ulcers.

Then follow the branches concerned with (2) the diseases of the eyes, ears, mouth, and nose, (3) general (systemic) diseases, such as fever, dysentery, insanity, hysteria, leprosy, and unnatural discharges, (4) demoniacal diseases and incantation and exorcism, (5) management of children, (6) toxicology, the elimination of natural or artificial poisons, (7) the science of rejuvenation and prolongation of life, and finally, (8) the science of aphrodisiacs.

The primary importance of surgery among these 8 branches of healing is stated succinctly:

> All hold this Tantram [branch] to be the most important of all the other branches of the Ayurveda, inasmuch as instantaneous actions can be produced with the help of such appliances as surgical operations, external applications of alkalis, cauterisation, etc., and secondly inasmuch as it contains all that can be found in the other branches of the science of medicine as well, with the superior advantage of producing instantaneous effects by means of surgical instruments and appliances. Hence it is the highest in value of all the medical Tantras. It is eternal and a source of infinite piety, imparts fame and opens the gates of Heaven to its votaries, prolongs the duration of human existence on earth, and helps men in successfully fulfilling their missions, and earning a decent competence, in life.[2]

The great flowering of surgery in early Indian medical history is particularly significant in view of the obstacles that stood in the way of the study of anatomy. According to the Hindu tenets the human body is sacred in death. It may not be violated by dissection and according to the injunction of the Hindu

laws the corpses of all persons more than 2 years old must be cremated in their original condition. Contact with the corpse other than that necessary in the act of cremation would also have defiled the dissector himself. It is obvious, however, that Sushruta did have some anatomic knowledge, although it was of a vague and inexact nature. This was gained in two manners. One was to take the injunction concerning cremation literally and to confine dissection to bodies of children under 2 years of age. This custom probably accounts for the multitude of bones (between 300 and 360) said to exist in the human skeleton, for individual parts of the bones which had not yet fused were enumerated. The other way of obtaining anatomic knowledge was pursued secretly and only when unclaimed bodies were found. These were left lying in a shallow running brook for 7 days, then the macerated flesh was removed with wisk brooms and the exposed inner parts inspected, with no hand ever actually touching the body. The anatomic knowledge so gained was far from accurate and was generally confined to an enumeration and classification of the constituent parts.

The physiologic concepts underlying the *Sushruta Samhita* are even less suited than those of anatomy to furnish the basis of a rational surgical text. Like all other contributors to Ayurvedic medicine, Sushruta believed the body to be permeated and activated by 3 humoral elements—air, phlegm, and bile. Harmony in the elementary substances brought health; imbalance, disease. But while seemingly heeding this system, Sushruta recognized other etiologic factors as well. His definition of disease is actually quite broad when he says, "Man is the receptacle of any particular disease, and that which proves a source of torment or pain to him, is denominated as disease. There are four different types of disease such as, Traumatic, or of extraneous origin, Bodily, Mental, and Natural."[3] The "Bodily" diseases are related to food and drink, to the blood, or the humors. Excessive hostility, joy, fear, or other emotions produce "Mental" diseases, while the "Natural" diseases are caused by physical wants and the process of aging.

Though it was considered the foremost of the medical arts, surgery was reserved as the last recourse in combating illness. Sushruta, the surgeon, was thus completely conversant with all other branches of therapy including diet and hygiene, which were greatly stressed, and pharmacology with its tremendous supply of vegetable, animal, and mineral medicaments. Sushruta lists 760 healing plants that were known to him. Of great and general medical importance, and of particular interest to medical readers, was the selection and training of the physician-surgeon:

> . . . The formal initiation of a pupil into the science of medicine . . . should be imparted to a student, belonging to one of the three twice-born castes such as, the Brahmana, the Kshatriya, and the Vaishya, and who should be of tender years, born of a good family, possessed of, a desire to learn, strength, energy of action, contentment, character, self-control, a good retentive memory, intellect, courage, purity of mind and body, and a simple and clear comprehension, command a clear insight into the things studied, and should be found to have been further graced with the necessary qualifications of thin lips, thin teeth and thin tongue, and possessed of a straight nose, large, honest, intelligent eyes, with a benign contour of the mouth, and a contented frame of mind, being pleasant in his speech and dealings, and usually painstaking in his efforts. A man possessed of contrary attributes should not be admitted into (the sacred precincts of) medicine."[4]

Upon the extremely formal ritual of initiation the newly accepted disciple was given the following solemn injunction by his preceptor:

> Then having thrice circumambulated the sacrificial fire, and having invoked the fire god to bear testimony to the fact, the preceptor should address the initiated disciple as follows: "Thou shalt renounce lust, anger, greed, ignorance, vanity, egotistic feelings, envy, harshness, niggardliness, falsehood, idleness, nay all acts that soil the good name of a man. In proper season thou shalt pair thy nails and clip thy hair and put on the sacred cloth, dyed brownish yellow, live the life of a truthful, self-controlled anchorite and be obedient and respectful towards thy preceptor. In sleep, in rest, or while moving about—while at meals or in study, and in all acts thou shalt be guided by my directions. Thou shalt do what is pleasant and

beneficial to me, otherwise thou shalt incur sin and all thy study and knowledge shall fail to bear their wished-for fruit, and thou shalt gain no fame. If I, on the other hand, treat thee unjustly even with thy perfect obedience and in full conformity to the terms agreed upon, may I incur equal sin with thee, and may all my knowledge prove futile, and never have any scope of work or display. Thou shalt help with thy professional skill and knowledge, the Brahmanas, thy elders, preceptors and friends, the indigent, the honest, the anchorites, the helpless and those who shall come to thee (from a distance), or those who shall live close by, as well as thy relations and kinsmen (to the best of thy knowledge and ability), and thou shalt give them medicine (without charging for it any remuneration whatever), and God will bless thee for that. Thou shalt not treat medicinally a professional hunter, a fowler, a habitual sinner, or him who has been degraded in life; and even by so doing thou shalt acquire friends, fame, piety, wealth and all wished for objects in life and thy knowledge shall gain publicity."[5]

Diagnosis, though connected with the humoral theories in a general manner, was not restricted to speculations. Sushruta gave explicit instructions concerning inspection, palpation and auscultation, the use of taste and smell, the interpretation of dreams, and the interrogation of the patient and his family concerning the patient's habits, their deviation in disease, and all subjective symptoms.

A physician having thoroughly studied the Science of Medicine, and fully pondered on and verified the truths he has assimilated, both by observation and practice, and having attained to that stage of (lucid) knowledge, which would enable him to make a clear exposition of the science (whenever necessary), should open his medical career (commence practising) with the permission of the king of his country. He should be cleanly in his habits and well shaved, and should not allow his nails to grow. He should wear white garments, put on a pair of shoes, carry a stick and an umbrella in his hands, and walk about with a mild and benignant look as a friend of all created beings, ready to help all, and frank and friendly in his talk and demeanour, and never allowing the full control of his reason or intellectual powers to be in any way disturbed or interfered with.[6]

Sushruta also touches upon the diagnosis of diabetes mellitus, first made in India, by pointing out not only the sweet taste of urine but also the fact that the sweetness of the discharge could be inferred from its attraction of flies and ants.

The importance of diagnosis was matched by that of prognosis, although the latter was not restricted to the rational ways of the former. Sushruta's chapters on prognosis are an amazing mixture of medical predictions and irrational portents. The observation of physical changes and symptoms presaging recovery or death was interchanged with a study of the messenger, omens, and dreams, all of which could augur well or badly for the patient's recovery. The emphasis on prognosis was not only for the benefit of the patient and his family but even more for the sake of the physician, who was free and even definitely advised by Sushruta to cease treatment of an incurable disease in order to avoid the taint upon his reputation of a fatality.

Sushruta divided surgical operations into 8 categories, (1) *incision* for "ailment due to the lodgment of a foreign body in the flesh or a bone," (2) *excision,* "in swellings in general diseases affecting the mammary organs . . . and diseases which are caused by suppuration in the local flesh or any soft part of the body (such as fistula in ano) as well as stone in the bladder and diseases due to a derangement of the fat," (3) *scarification,* (4) *aspiration* to be used in connection with a vein, abdominal dropsy, hydroceles, and ulcers containing foreign matter, (5) *extraction* of morbid or foreign matter, bladder stones, feces from the constricted anus, or fetus from the uterus, (6) *secreting or evacuating measures,* to be employed in the case of pain or inflammatory swellings restricted to particular parts of the body, elephantiasis, blood poisoning, tumors, erysipelas, and so forth, (7) *probing* in fistulas, and (8) *suturing* with threads of flax, sinews, and hair. The needles for suturing were minutely described and graded in length and thickness according to the nature of the lesion.

The needle should not be pricked into a part too near, or too remote from the fissure, or the mouth of an ulcer, as there might be the danger of the suture being broken off (at the least pressure or movement) in the first instance and of genesis of pain in the second. An ulcer, thus

properly sutured, should be covered over with cotton and dusted over with a pulverised compound . . . or with the ashes of a burnt piece of Kshauma cloth, or with the powders of the Shallaki fruit. Then the ulcer should be properly bandaged, and measures and rules regarding the regimen of diet, and conduct previously laid down in the chapter on the nursing of an ulcer-patient should be adopted and observed.[7]

In the *Sushruta Samhita* 101 blunt and 20 sharp instruments are listed and described. Among the former were varieties of forceps, pincers, tubes, books, catheters, and sounds, as well as magnets for the extraction of foreign bodies. The hand, however, is considered the most important instrument, for without it no operation can be performed. The sharp instruments consisted of lancets, knives, bistouries, scissors, needles, trocars, and saws. The instruments were made of steel, the manufacture of which was long understood by the Indians, and they were kept in wooden boxes.

Cauterization by escharotics, hot metal, or boiling fluids was considered to be more effective than intervention by means of the knife. Red-hot needles were inserted into the parenchyma of the spleen in order to treat splenic enlargement. Fourteen different types of dressings were listed, made of a variety of materials including cotton, wool, silk, and linen. Splints were fashioned from bamboo, branches of other trees, and bark. Bleeding was arrested by compression, herbs, and hot oil. Facial wounds were sutured. A certain amount of anesthesia was achieved by means of alcoholic intoxication. Both alcohol and meat, normally forbidden to Hindus, were not only permitted but became important factors in the treatment and the diet of Indian patients.

The *Sushruta Samhita* makes it evident that considerable mastery had been achieved in diagnosis, operative intervention, and after-treatment. Fractures, dislocations, the extirpation of tumors, the cauterization of fistulas, the removal of foreign bodies, and the performance of paracentesis were rationally and intelligently described. Ophthalmic surgery was extensively described. The lens was recognized as the seat of vision but the description of the operation for cataract lacks the clarity of descriptions of other operative procedures. It is noteworthy that the practice of gynecology and obstetrics fell into the category of surgery. Explicit and highly intelligent directions were given for the regimen and diet of the mother during pregnancy and the lying-in period, as well as for the newborn child. Cesarean section after death and embryotomy in case of fetal death were also practiced. The most outstanding achievements of Indian surgery, however, are recorded in the chapters on lithotomy, laparotomy, and plastic surgery. The great stride in and need for the latter type of operation grew out of the practice of punishing many and even slight offenses by the amputation of noses and ears. Although, as mentioned earlier, the question of reciprocal influences of Indian and Western medicine in general has never been completely answered, it is an established fact that Indian plastic surgery provided the basic pattern for Western efforts in that field.

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